IUCLID

Data Set

Existing Chemical	:	ID: 2778-42-9
CAS No.	:	2778-42-9
EINECS Name	:	1,3-bis(1-isocyanato-1-methylethyl)benzene
EC No.	:	220-474-4
Molecular Formula	:	C14H16N2O2

Producer related part

Company	:	Cytec Industries Inc.
Creation date	:	21.01.2005

Substance related part

Company	:	Cytec Industries Inc.
Creation date	:	21.01.2005
Status	:	
Memo	:	
Printing date	:	27.01.2005
Revision date	:	
Date of last update	:	15.03.2005
Number of pages	:	63
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	manufacturer
Name	:	Cytec Industries Inc.
Contact person	:	Randy Deskin, Ph.D, DABT
Date	:	07.02.2005
Street	:	5 Garret Mountain Plaza
Town	:	07424 West Patterson, NJ
Country	:	United States
Phone	:	(973) 357-3372
Telefax	:	
Telex	:	
Cedex	:	
Email	:	Randy.Deskin@cytec.com
Homepage	:	

07.02.2005

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name	:	1,3-bis(1-isocyanato -1-methylethyl)benzene
Smiles Code	:	O=C=NC(c1cc(ccc1)C(N=C(=O))(C)C)(C)C
Molecular formula	:	C14 H16 N2 O2
Molecular weight	:	244.30
Petrol class	:	

21.01.2005

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	typical for marketed substance
Substance type	:	organic
Physical status	:	liquid
Purity	:	>= 99 % w/w
Colour	:	colorless
Odour	:	

24.01.2005

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

1,3-Bis(1-isocyanato-1-methylethyl benzene

21.01.2005

Benzene, 1,3-bis(1-isocyanato-1-methylethyl)-

21.01.2005

1,3-Bis(1-isocyanato-1-methylethyl)benzol

21.01.2005

1,3-bis(1-isocianato-1-metiletil)benceno

21.01.2005

a,a,a',a'-Tetramethyl-m-phenylenedimethylene diisocyanate

21.01.2005

a,a,a',a'-Tetramethyl-m-xylylene diisocyanate

21.01.2005

1,3-Bis(a-isocyanatoisopropyl)benzene

21.01.2005

Isocyanic acid, a,a,a',a'-tetramethyl-m-xylylene ester

21.01.2005

Isocyanic acid, m-phenylenediisopropylidene ester

21.01.2005

m-Bis(1-isocyanato-1-methylethyl)benzene

21.01.2005

TMXDI

21.01.2005

Tetramethyl-m-xylylene diisocyanate

21.01.2005

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : industrial
Category : Chemical industry: used in synthesis

Remark : TMXDI is used as an industrial intermediate that is incorporated into various polymers to improve performance. Application areas for the polymers incorporating TMXDI include specialty coatings, aqueous dispersions, automotive coatings, wood coatings, inks, sealants, adhesives, thermoplastic urethanes, and lacquers.

TMXDI imparts improved physical properties to polyurethane products, affording higher strength and improved adhesion, appearance, and flexibility, resulting in more durable products. Common commercial products that may have been made using TMXDI include, fabric and leather finishes, adhesives, automotive paints, printing inks, sealants, and wood coatings.

TMXDI is FDA approved for use in food-packaging under specific listings in the Code of Federal Regulations (CFR) Title 21-Food and Drugs Chapter I-Food and Drug Administration, Department of Health and Human Services.

21.01.2005

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

Origin of substance : Synthesis
Type : Production

21.01.2005

1.8 REGULATORY MEASURES

Type of measure :
Legal basis : other

Remark : 21 CFR, PART 175-Indirect Food Additives: Adhesives and Components of Coatings-- §175.105 (ADHESIVES). Clears meta-tetramethyl xylene diisocyanate for reaction with one or more of the polyols and polyesters listed in §175.105 and dimethylolpropionic acid and triethylamine, N-methyldiethanolamine, 2-dimethylaminoethanol, 2-dimethyl-amino-2-methyl-1-propanol and/or 2-amino-2-methyl-1-propanol in the production of polyurethane resins intended for use as components of adhesive formulations used in food packaging applications.

Cytec Industries Petition Oct. 26, 1993, effective March 12, 1996.

21.01.2005

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value	:	= -10 °C
Decomposition	:	no, at °C
Sublimation	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Cytec Material Safety Data Sheet for TMXDI® (Meta) Aliphatic Isocyanate, MSDS# 2344, dated 12/01/1999.
Test condition	:	Determined from Specific Heat measurements which were measured using a Perkin Elmer DSC 2 Differential Scanning Calorimeter and the technique of O'Neil with sapphire as the reference.
Reliability	:	(2) valid with restrictions The values from a collection of data are assigned areliability code of 2g according to the criteria established by Klimisch et al. (Regulato ry Toxicology and Pharmacology 25: 1-5, 1997) .
Flag	:	Critical study for SIDS endpoint

22.01.2005 (3)

2.2 BOILING POINT

Value	:	= 292 °C at 1013 hPa
Decomposition	:	no
Method	:	
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Cytec Material Safety Data Sheet for TMXDI® (Meta) Aliphatic Isocyanate, MSDS# 2344, dated 12/01/1999.
Test condition	:	Determined by calculation from the analytically determined vapor pressure using isotenoscope technique.
Test substance	:	Theoretical 100% CAS No. 2778-42-9
Reliability	:	(2) valid with restrictions The values from a collection of data are assigned a reliability code of 2g according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997).
Flag	:	Critical study for SIDS endpoint

22.01.2005 (3)

Value	:	= 320.1 °C at 1013 hPa
Decomposition	:	
Method	:	other: estimated
Year	:	2002
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Test condition	:	Estimated by the MPBPWIN Program (v.1.40), using the Adapted Stein and Brown Method.
Test substance	:	Theoretical 100% CAS No. 2778-42-9
Reliability	:	(2) valid with restrictions The boiling point calculated by an accepted method is assigned a reliability code of 2f according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology

25: 1-5, 1997).

26.01.2005 (15)

2.3 DENSITY

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	= .0043 hPa at 25 °C
Decomposition	:	no
Method	:	other (measured):ASTM D2879-83
Year	:	1986
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The vapor pressure is listed as 0.0032 mmHg at 25 °C
Reliability	:	(2) valid with restrictions The values from a collection of data are assigned a reliability code of 2g according to the criteria established by Klimisch et al. (Regulato ry Toxicology and Pharmacology 25: 1-5, 1997).
Flag	:	Critical study for SIDS endpoint

26.01.2005 (3)

Value	:	= .004 hPa at °C
Decomposition	:	
Method	:	other (calculated)
Year	:	2002
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Estimated by the MPBPWIN Program (v.1.40)3, using BP of 292°C and the Modified Grain Method.
Remark	:	The value is consistent with measured value.
Result	:	The result listed is 0.00298 mmHg at 25 °C.
Test substance	:	Theoretical 100% CAS No. 2778-42-9
Reliability	:	(2) valid with restrictions The vapor pressure calculated by an accepted method is assigned a reliability code of 2f according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997).

26.01.2005 (15)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water
Log pow	:	= 4.74 at °C
pH value	:	= 7
Method	:	other (calculated)
Year	:	2002
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Estimated by the KowWin Program (v.1.66)
Test substance	:	Theoretical 100% CAS No. 2778-42-9
Reliability	:	(2) valid with restrictions

The partition coefficient calculated by an accepted method is assigned a reliability code of 2f according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997).

Flag : Critical study for SIDS endpoint

26.01.2005 (15)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	= 5.833 mg/l at 25 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	other: calculated
Year	:	2002
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : Estimated from Kow with WSKOW (v1.40)1 : KowWin Estimate

Test substance : Theoretical 100% CAS No. 2778-42-9

Reliability : (2) valid with restrictions
The water solubility calculated by an accepted method is assigned a reliability code of 2f according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997).

Flag : Critical study for SIDS endpoint

26.01.2005 (15)

Solubility in	:	Water
Value	:	at °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	

Result : Insoluble, reacts slowly with water forming insoluble ureas.

Source : Cytec Material Safety Data Sheet for TMXDI® (Meta) Aliphatic Isocyanate, MSDS# 2344, dated 12/01/1999.

Reliability : (2) valid with restrictions
The values from a collection of data are assigned a reliability code of 2g according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997).

22.01.2005

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	Sun light
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	1500000 molecule/cm³
Rate constant	:	= .0000000000101332 cm³/(molecule*sec)
Degradation	:	= 50 % after 12.7 hour(s)
Deg. product	:	
Method	:	other (calculated)
Year	:	2002
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Estimated by the AopWin program (v1.90), which estimates rate constants and half-lives of atmospheric reactions of organic compounds with hydroxyl radicals and ozone in the atmosphere.
Result	:	For reaction with hydroxyl radicals, the predicted half-life of the chemical is relatively rapid.
Test substance	:	Theoretical 100% CAS No. 2778-42-9
Reliability	:	(2) valid with restrictions The photodegradation rate calculated by an accepted method is assigned a reliability code of 2f according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997).
Flag	:	Critical study for SIDS endpoint.

26.01.2005 (15)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	= .4 hour(s) at 25 °C
t1/2 pH7	:	= .4 hour(s) at 25 °C
t1/2 pH9	:	= .3 hour(s) at 25 °C
t1/2 pH 1.2	:	= 1 minute(s) at 37 °C
Deg. product	:	
Method	:	OECD Guide-line 111 "Hydrolysis as a Function of pH"
Year	:	2003
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Testing at pH 1.2 showed almost instantaneous hydrolysis at 37 degrees C, with only 3.45% of the fortified concentration remaining at the time zero analysis. The hydrolysis rate constants (s-1) at 25 degrees C were 4.70 E -4 at pH 4; 5.29 E-4 at pH 7; and 5.74 E -4 at pH 9.
Test condition	:	The test was carried out using Method 111 of the OECD Guidelines. Buffer solutions of hydrochloric acid and potassium chloride (for pH = 1.2); potassium hydrogen phthalate (for pH = 4); disodium hydrogen orthophosphate (anhydrous), potassium dihydrogen orthophosphate and sodium chloride (for pH = 7); and disodium tetraborate and sodium chloride (for pH = 9) were prepared. The buffer solutions were sterilized by passing through a 0.2 micron membrane filter. In addition, these solutions were

subjected to ultrasonication and degassing with nitrogen to minimize dissolved oxygen content.

Sample solutions were prepared in stoppered glass flasks at a nominal concentration of 1 x 10-3 g/l in the four buffer solutions. A 1% co-solvent of acetonitrile was used to aid solubility. The solutions were shielded from light while being maintained at the test temperature.In a preliminary test, sample solutions at pHs of 4, 7, and 9 were maintained at 50.0 +/- 0.5 degrees C for a period of 2.4 hours.

Results from the preliminary test showed it was necessary to undertake further testing at pH 4, pH 7, and pH 9, with solutions being maintained at 25 +/- 0.5 degrees C, and at pH 1.2 with a solution being maintained at 37 +/- 0.5 degrees C for 24 hours. In addition, a sample solution was prepared at pH = 1.2 using a buffer solution of hydrochloric acid and potassium chloride. This solution was maintained at 37.0 +/- 0.5 degrees C for 24 hours.

Aliquots of the sample solutions were taken from the flask at various times and the pH of each solution recorded. The concentration of material in each sample solution was determined by high performance liquid chromatography (HPLC).

Duplicate aliquots, (50 ml)(where possible due to time constraints, i.e. fast degradation) of each sample were passed through a previously primed C18 solid phase extraction (SPE) cartridge. The cartridges were then driedwith nitrogen and the analyte eluted with acetonitrile (5ml).

Duplicate standard solutions of test material were prepared in acetonitrile at a nominal concentration of 10 mg/l.

The concentration of the sample solutions (g/l) was calculated using the following equation:

C(spl) = P (spl)/P (std) x C (std) x D x 1/1000,

where C(spl) = sample concentration (g/l); P(spl) = mean peak area of sample solution; P(std) = mean peak area of standard solution, corrected to nominal standard concentration; C(std) = nominal standard concentration (10 mg/l).

Graphs of the common logarithm of the concentration (g/l) versus time (hours) were plotted for pH 4, pH 7 and pH 9 at 25 degrees C, and the rate constant and half-life calculated using the following equations.

k(obs) = -slope x 2.303 and t(1/2) = 0.693/k(obs),

where k(obs) = rate constant (hours) and t(1/2) = half-life (hours).

The linearity of the detector response with respect to concentration was assessed over the nominal concentration range of 0 to 20 mg/l, and found to be satisfactory with a correlation coefficient of 1.000 being obtained.

Test substance : The test substance (Lot number UC1081701) was of 99.29% purity.
Reliability : (1) valid without restriction
Well-conducted guideline study following GLP.
Flag : Critical study for SIDS endpoint
26.01.2005 (22)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : fugacity model level III
Media : other: air, water, soil, sediment
Air : .779 % (Fugacity Model Level I)
Water : 18.1 % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : 18.5 % (Fugacity Model Level II/III)
Soil : 62.6 % (Fugacity Model Level II/III)
Method : other: calculated
Year : 2002

Remark : Inputs to the program are CAS No. 2770-42-9, a melting point of -10 degrees C, a boiling point of 292 degrees C and a vapor pressure of .0032 mm Hg. Default values of 1000 kg/hr emissions to air, water and soil were used for the primary concentration values estimated for the various media. A Henry's Law Constant of 3.22 E-6 atm-m3/mole was obtained (bond estimate). Half-lives in various media were: air = 25.3 hours, water = 1440 hours, soil = 1440 hours, and sediment = 5 760 hours.

The Level III fugacity model was also run with the same inputs as above, but varying the assumed emission rates. The results are shown below:

Medium	Concentration %	Emissions (kg/hr)
Air	30.3	1000
Water	10.4	0
Soil	48.7	0
Sediment	10.6	0

Medium	Concentration %	Emissions (kg/hr)
Air	0.0401	0
Water	49.5	1000
Soil	0.0646	0
Sediment	50.4	0

Medium	Concentration %	Emissions (kg/hr)
Air	0.000324	0
Water	0.034	0
Soil	99.9	1000
Sediment	0.0346	0

Test substance : Theoretical 100% CAS No. 2778-42-9
Reliability : (2) valid with restrictions
The fugacity calculated by an accepted method is assigned a reliability code of 2f according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997).
Flag : Critical study for SIDS endpoint
27.01.2005 (15)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	activated sludge
Concentration	:	2 mg/l related to Test substance
Contact time	:	28 day(s)
Degradation	:	= 13.7 (±) % after 28 day(s)
Result	:	other: not readily biodegradable
Control substance	:	Aniline
Kinetic	:	% %
Deg. product	:	
Method	:	OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year	:	1988
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The test material was not found to be readily biodegradable by the OECD Closed Bottle Test. Degradation after 28-days was determined to be 13.7% as compared to 95% for the Aniline reference material. Because a level of 70% was not reached, this substance is not "Readily Biodegradable" by this test procedure.
Test condition	:	Due to the insolubility of the test article, sample aliquots were micro-pipetted onto a disc of glass fiber filter, which was then added directly to the test vessel. This ensured the immersion of the sample in the dilution water, increased surface area of exposure and avoided surface file and escape resulting from water partitioning. The solution was inoculated with a low concentration of microorganisms from a mixed population and kept in closed bottles in the dark at a constant temperature of 20 ± 1 degrees C. The activated sludge bacteria was from Bergen Co. New Jersey. The degradation was followed by oxygen analyses with the YSI Dissolved Oxygen Analyzer 54A over a 28-day period. A parallel control with inoculum, but without test material, was run as a blank correction factor. The procedure was validated by means of a reference substance (2 mg/l aniline) of known biodegradability.
Reliability	:	(1) valid without restriction GLP guideline studies are assigned a reliability code of 1a according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997).
Flag	:	Critical study for SIDS endpoint

26.01.2005 (21)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Lepomis macrochirus (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
NOEC	:	> 52.19
LC50	:	> 65.88
Limit test	:	no
Analytical monitoring	:	yes
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	1993
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Remark : In general, the material persisted at eighty percent or greater when calculated measured values were compared. Total mortality was observed in one replicate of the 1.0 g/L treatment. Since no other mortality occurred during the 96-hour period, it is believed that the mortalities were caused by contamination of the test chamber.

The NOEC and LD50 values are based on exposure to Water Accommodating Fraction, measured by analysis.

Test condition : Exposure Conditions: -22.3 C, continuously monitored.
Diurnal light: ~15 hours light: ~ 9 hours dark with a gradual intensity conversion between periods. Daylight intensity ranged from 61.74 to 63.61 footcandles during full daylight periods.

Test conduct: The static fish bioassay was conducted in 8.5L glass vessels containing 3.2 liters Laboratory Dilution Water. Twenty (10 per 2 replicates) fish with a mean weight of 0.209 g and a mean length of 26 mm were used for each test concentration. A 48-hour range-finding test was conducted to determine the concentration range for the definitive study. The preliminary test concentrations were set at 0.005 g/L, 0.01 g/L, 0.05 g/L, 0.1 g/L, and 1.0 g/L. Ten percent mortality was observed in the 0.1 g/L treatment after 48 hours. No mortality occurred in the remaining treatments during the 48-hour exposure period.

Based on the results of the preliminary testing, five test concentrations were selected. The nominal treatment levels for the test were 0 (laboratory dilution water control), 0.06, 0.12, 0.25, 0.5, and 1.0 g/L. Individual treatments were prepared by adding the appropriate amount of test material to laboratory dilution water. Each treatment was slowly mixed (<10% vortex) on a magnetic stirplate with a teflon coated stirbar for approximately 48 hours. During mixing, clear globules of the test material were observed throughout the water column. An oily surface slick was also observed in all treatments. After the mixing period the water column appeared clear with clear globules of test material on the bottom. The water accommodating fraction (WAF) of each treatment solution was siphoned from the middle portion of the mixing container and divided into 2 replicate chambers. Test chambers were covered with glass to minimize evaporation and/or volatilization.

The fish were observed once every 24 hours for mortality and abnormal effects. Water quality parameters of temperature, dissolved oxygen and pH were measured throughout the test and were within acceptable limits. The measured parameters were as follows: Dissolved oxygen concentrations ranged from 5.3 to 8.0 mg/L. The pH values ranged from 7.0 to 7.8. Test vessel temperatures were kept constant at 22-23 degrees C.

Samples of the test material solutions were analyzed for Dissolved Organic Carbon (DOC) content (APHA, American Water Works Association and Water Pollution Control Federation. 1989. Standard Methods for the Examination of Water and Wastewater, 17th ed. American Public Health Association, Washington, D.C. Method 5301B, Combustion-Infrared). DOC results were obtained by filtering the samples through a 0.45 um teflon filter and analyzing for Total Carbon (TC) and Inorganic Carbon (IC) with the difference between the two values considered DOC. Samples were analyzed using a Dorhmann DC-190 Total Organic Carbon Analyzer.

To evaluate the persistence of the test material during the test, the calculated measured values at termination were compared to the initial calculated measured values.

Nominal Chemical Conc. (g/L)	Measured Chemical DOC (ppm) Day 0 *	Day 4	Concentration (mg/L)** Day 0	Day 4
Control	5.408	3.878	-	-
0.06	10.07	12.19	6.772	12.07
0.12	41.27	42.9	52.09	56.68
0.25	24.25	23.57	27.37	28.60
0.5	45.51	35.63	58.25	46.12
1.0	45.46	54.53	58.18	73.58

(*) Samples stored at room temperature overnight and analyzed on Day 1, 2-Mar-93.
Note: Test Material is 68.84% carbon.
(**) Treatment levels were converted from nominal values to measured values in the following manner:
(Treatment DOC value - Control DOC value)/ % carbon of the test material

Test substance : Purity of the test material was approximately 99%.
Reliability : (1) valid without restriction
This study is assigned a reliability code of 1a according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997). Guideline study.
Flag : Critical study for SIDS endpoint
26.01.2005 (16)

Type : static
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
NOEC : = .32
LC50 : = .67
Limit test :
Analytical monitoring : no
Method : other
Year : 1986
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Based on methods outlined in the Committee on Methods for Toxicity Test with Aquatic Organisms, USEPA 660/3-75009. ABC Laboratories Protocol 7601.
Test condition : The static fish bioassay was conducted in five gallon glass vessels containing 15 liters of soft reconstituted water. 10 fish with a mean weight of 0.099 g and a mean length of 19 mm were used for each test concentration. The test vessels were kept in a water bath at 22 (±1) C. 24- and 48-hour range-finding tests were conducted to determine the concentration range for the definitive study. The preliminary test concentrations were set at 1.0, 10.0, and 100 mg/L and at 0.01, 0.1 and 1.0

mg/L. The test material was dissolved in acetone. Based on the results of the preliminary testing, five test concentrations were selected, 0.10, 0.18, 0.32, 0.56, and 1.0 mg/L. Also included was a dilution water control and a solvent control. The solvent control chamber received a 1.5 ml aliquot of acetone, which was equivalent to the highest amount used in any test solution.

Test concentrations were prepared by preparing a stock solution in deionized water and serially diluting to obtain desired concentration. The 0.32, 0.56 and 1.0 mg/L solutions had a very light surface film after stirring but the film was no longer visible after 24 hours of testing. All results were based on the nominal concentrations.

The fish were observed once every 24 hours for mortality and abnormal effects. Water quality parameters of temperature, dissolved oxygen and pH were measured throughout the test and were within acceptable limits. The measured parameters were as follows: Dissolved oxygen concentrations ranged from 4.9 to 9.2 mg/L; these values represented 56 to 105% saturation at 22C. The dissolved oxygen decreased slightly (56% saturation) in the highest test concentration, as compared to the controls at 96 hours. The pH values ranged from 6.9 to 7.7. The test vessels were kept in a water bath at 22 +/- 1C throughout the study. The 24-, 48-, and 96- hour LC50 values for TMXDI were 0.70, 0.67, and 0.67 mg/L, respectively. The no-effect concentration for the test material, based on the lack of mortality and abnormal effects, was estimated to be 0.32 mg/L after 96 hours. The abnormal effects of mortality, surfacing, loss of equilibrium and/or quiescence were observed in the 0.56 and 1.0 mg/L concentrations during the 96-hr period. Statistical analysis of the concentration vs. effect data was obtained by employing a computerized LC50 program developed by Stephan, et al. (A computer program for calculating an LC50. U.S. E.P.A., Duluth, Minnesota, pre-publication manuscript, August, 1978). This program calculated the LC50 statistic and its 95% C.L. using the binomial and the moving average tests, respectively. The method of calculation selected for use was that which gave the narrowest confidence limits for the LC50.

Test substance : Purity of the test material was 98-99%.
Reliability : (1) valid without restriction
GLP guideline studies are assigned a reliability code of 1a according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997).
Flag : Critical study for SIDS endpoint
26.01.2005 (1)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
NOEC	:	< 1
EC50	:	= 5.2
Limit Test	:	no
Analytical monitoring	:	no
Method	:	other
Year	:	1986
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : Based on methods outlined in the Committee on Methods for Toxicity Test with Aquatic Organisms, USEPA 660/3-75009. ABC Laboratories Protocol

7806.

Remark : The results are listed as LC50 values, rather than EC50 values. The 24-hour LC50 value is 6.5 mg/L.

Test condition : The static Daphnia magna bioassay was conducted in 250 ml glass beakers, 10 daphnids/ beaker, containing 200 ml of ABC well water. These vessels were kept at 20 (± 2) degrees C. The lighting was maintained at 50-70 foot-candles on a 16 hour daylight photoperiod. An initial range-finding test was conducted to determine the concentration range for the definitive study. The preliminary test concentrations were set at 1.0, 10 and 100 mg/L. The material was dissolved in acetone.

Based on the results of the preliminary testing, five test concentrations were selected and tested in duplicate, 0 (control), solvent control, 1.0, 1.8, 3.2, 5.6, and 10 mg/L. The solvent control received an aliquot of 0.020 ml of acetone equivalent to that added to the highest test concentration. Test concentrations were prepared by preparing a stock solution in deionized water and serially diluting to obtain desired concentrations. All results were based on the nominal concentrations. Water quality parameters of temperature, dissolved oxygen and pH were measured at the termination of the test and were within acceptable limits. The dissolved oxygen concentrations, which ranged between 8.2 and 8.9 mg/l, were considered adequate for testing. The pH values of the treated chambers were consistent with the control and ranged form 8.2 to 8.3. The no-effect concentration based on the lack of mortality and abnormal effects was <1.0 mg/l after 48 hours, since the abnormal effects of mortality, quiescence, surfacing and/or daphnids lying on the bottom were observed in all test concentrations. The single mortality in the control was considered aberrant. The 24- and 48-hour LC50 values for TMXDI were 6.5 and 5.2 mg/L. Statistical analysis of the concentration vs. effect data was obtained by employing a computerized LC50 program developed by Stephan, et al. (A computer program for calculating an LC50. U.S. E.P.A., Duluth, Minnesota, pre-publication manuscript, August, 1978). This program calculated the LC50 statistic and its 95% C.L. using the binomial and the moving average tests. The method of calculation selected for use was that which gave the narrowest confidence limits for the LC50.

Test substance : Purity of the test material was 98-99%.

Reliability : (1) valid without restriction
GLP guideline studies are assigned a reliability code of 1a according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997).

Flag : Critical study for SIDS endpoint
26.01.2005 (2)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Selenastrum capricornutum (Algae)
Endpoint	:	growth rate
Exposure period	:	96 hour(s)
Unit	:	mg/l
NOEC	:	= .34
EC50	:	= 2.1
Limit test	:	no
Analytical monitoring	:	no
Method	:	OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year	:	1987
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Result : Linear regression analysis, plotting percent growth versus log of concentration, yielded a 96 hr EC50 of 2.1 ppm and a NOEC of 0.34 ppm.

Cell growth was insufficient at 24 and 48 hours to establish concentration-effect relationships for all concentrations and for the blank control. The median effects, therefore, could not be calculated for these time periods.

The calculated correlation coefficients indicate that the 96hr value may be the better estimate of the median algal inhibitory concentration due to more developed cell growth with time and thus better enumeration and differentiation among test concentrations.

The rate of cell growth was satisfactory (greater than 16 x inoculum level at 72 hrs) in controls for acceptable data transformation. The use of the solvent produced a slight "lag" in the growth of cells but did not depress the population to a degree severe enough to confound the concentration effects.

Test condition : Temperature and light readings were measured throughout the test and were within acceptable limits. The static algal toxicity study on Selenastrum capricornutum (Strain #22662) was conducted in 250 mL Erlenmeyer flasks containing 100 mL of Sterile OECD Algal nutrient medium. This media was composed of 10.0 mL of a salt solution diluted to a final volume of 1,000 mL of deionized water. To each flask was added a starting algal inoculum containing 1 ×104 cells/ml. The test vessels were incubated for 96 hours at 21-22 ± 2°C under continuous "cool white" fluorescent light (approximately 8000 Lux) and constant shaking. Temperature and light intensity were monitored throughout the study. Based on the results of the range-finder, test concentrations were set at 0, 0.32, 1.0, 3.2, 10.0, and 32 mg/L. The test material was diluted in anhydrous acetone v/v and stored in dark until use. Test concentrations were prepared by preparing a stock solution in deionized water and serially diluting to obtain desired concentration. Controls contained 10 microliters of acetone. Maximum dissolved solvent added was 10 microliters/flask. Test flasks were prepared in triplicate for each test concentrations and the control.

Test substance : Purity of the test material was 97-98%.

Reliability : (1) valid without restriction
GLP guideline studies are assigned a reliability code of 1a according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997).

Flag : Critical study for SIDS endpoint

27.01.2005 (20)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type : LD50
Value : = 5000 ml/kg bw
Species : rat
Strain : Sprague-Dawley
Sex : male/female
Number of animals : 60
Vehicle :
Doses : 2.8, 3.6, 4.5, 5.6, and 7.1 ml/kg
Method : other
Year : 1981
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Result : The results are listed in the following table:

Dose Level	Males Dead	Day of Death	Females Dead	Day of Death	Total Dead
0	0/5	-	0/5	-	0/10 (0%)
2.8	0/5	-	2/5	3	2/10 (20%)
3.6	0/5	-	1/5	3	1/10 (10%)
4.5	2/5	2,4	3/5	2	5/10 (50%)
5.6	3/5	2,3	2/5	2,4	5/10 (50%)
7.1	5/5	3	5/5	2,3	10/10 (100%)

The LD50 of the test article was calculated by the Method of Litchfield and Wilcoxon, 1949 as 5.0 (4.4 to 5.7) ml/kg for males and 4.6 (2.5 to 8.4) ml/kg for females. Male and female data were compared for deviations for parallelism and differences in potency. Because there were no statistically significant ($p > 0.05$) differences, male and female data were combined. The combined LD50 from the test article was 5.0 (4.0 to 6.2) ml/kg. The figures in parentheses are the 95% confidence limits.

Mean body weight data were compared between untreated and treated animals, treated animals gained less weight than controls and lost weight for 1 to 3 days post-dosing.
Mean Body Weight Data (grams)

Dose Level	Sex	Day -1	Day 1	Day 2	Day 3	Day 4	Day 7	Day 11	Day 15	Change
0.0	Male	246	228	246	253	264	284	306	320	+92
	Female	200	181	195	200	207	216	223	232	+51
2.8	Male	243	225	215	211	214	242	257	290	+65
	Female	189	174	163	158	171	184	187	207	+33
3.6	Male	243	225	214	217	225	246	256	284	+59
	Female	182	167	161	164	171	183	188	194	+28
4.5	Male	237	219	200	193	201	224	233	261	+46
	Female	192	175	163	159	163	193	199	205	+31
5.6	Male	248	228	211	212	216	238	259	295	+62
	Female	189	171	170	164	163	184	175	204	+36
7.1	Male	241	223	202	-	-	-	-	-	-
	Female	194	179	164	-	-	-	-	-	-

Clinical signs did not appear to increasein frequency or variety with increased dose level, did not exhibit any sex related trends, and included diarrhea, crusty material around anus, soft stool, crusty material around face, paws, eyes, nose, and scrotum, cream-colored material around mouth, alopecia, swollen feet, edema around anus, nasal discharge, red-colored nasal discharge, tachypnea, lacrimation, lethargy, urine-soaked fur, piloerection, ataxia, moribund, cold body temperature, and tremors. Untreated controls appeared normal throughout study.

Necropsy findings did not exhibit any apparent dose related or sex related trends.

Test condition : Animals were housed individually at room temperature, and fasted overnight before dosing. Sixty rats (5/per sex/per dose) received neat TMXDI by gavage at a concentrations of 0, 2.8, 3.6, 4.5, 5.6, and 7.1 ml/kg. Animals were observed frequently post-dosing and twice daily thereafter for physical condition and mortality. Physical examinations were performed pre-dose. Body weights were recorded on days -1, 1, 2, 3, 4, 7, 11, and 15 or at time of death if prior to scheduled termination of study. All animals found dead or surviving to day 15 were subjected to a complete gross necropsy.

Test substance : Purity of the test material was 91.58%.

Reliability : (1) valid without restriction
This study is assigned a reliability code of 1d according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997). Meets generally accepted scientific standards and is described in sufficient detail.

Flag : Critical study for SIDS endpoint

26.01.2005 (9)

Type : LD50
Value : > 5000 mg/kg bw
Species : rat
Strain : Sprague-Dawley
Sex : male/female
Number of animals : 10
Vehicle :
Doses :
Method : other: Pilot Oral Gavage LD50 Toxicity Study in Rats
Year : 1981
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Result : No signs of toxicity were observed on the day of dosing. Soft feces, inactivity, wet peri-anal area, crusty muzzle were noted in most of the animals from day 1 through day 3. The wet per-anal area persisted to termination of the 15-day study. Two females were found dead on day 2 of this study. Signs of toxicity observed prior to death were sedation, soft feces and wet peri-anal area. Postmortem examination revealed irritation of the intestinal mucosa. With the exception of these two females, all other animals showed an overall weight gain. Gross postmortem examination of the 8 survivors at terminal sacrifice revealed irritation of the small intestinal mucosa in 3 animals. There were no other significant findings attributable to TMXDI.

Test condition : Animals were housed individually at room temperature, and fasted overnight before dosing. Test material was administered undiluted. Ten rats (5/sex) received neat TMXDI by gavage at a concentration of 5000 mg/kg. Animals were observed at 20 minutes, 1 hour, 2 hours, and 4 hours post-dosing and twice daily through day 13 for physical condition and mortality. Physical examinations were performed pre-dose. Body weights were recorded on days -1, 0, 1, 2, 3, 6, 10, and 14. All animals surviving to day 15 were subjected to a complete gross necropsy by examining the

organs of the thoracic, abdominal, and cranial cavities.

Reliability : (2) valid with restrictions
This study is assigned a reliability code of 2e according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997). It was not conducted under GLP or OECD guidelines but generally meets scientific standards, is well documented and is accepted for assessment.

26.01.2005 (5)

5.1.2 ACUTE INHALATION TOXICITY

Type : LC50
Value : = 0.027 mg/L
Species : rat
Strain : Sprague-Dawley
Sex : male/female
Number of animals : 50
Vehicle :
Doses : 0.316, 0.935, 0.0533 and 0.02 mg/L
Exposure time : 4 hour(s)
Method : OECD Guide-line 403 "Acute Inhalation Toxicity"
Year : 1995
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Result : The mortality data is summarized as follows:

Group	Males	Females	Total
Group 1: Control	0/5	0/5	0/10
Group 2: 0.316 mg/L	5/5	5/5	10/10
Group 3: 0.0935 mg/L	5/5	5/5	10/10
Group 5: 0.0533 mg/L	5/5	4/5	9/10
Group 6: 0.02 mg/L	2/5	1/5	3/10

Clinical signs observed during exposure to TMXDI included respiratory abnormalities (exaggerated respiratory movements and/or irregular respiration), a partial closing of the eyes and a reddening of the ears and feet. Additional signs seen in rats exposed at 0.316 mg/L included piloerection, wet fur and restless behavior. During the observation period clinical signs included death, respiratory abnormalities (exaggerated respiratory movements, noisy respiration and/or gasping) a partial closing of the eyes and peripheral vasodilation. In addition, whole-body hypothermia, a red/brown discharge from the snout, immobility, emaciation, a swollen abdomen, lethargy, a dark appearance of the eyes, salivation, red/brown staining around the snout and jaws, wet fur around the snout, jaws and the head, and matted appearance of the fur were seen in some groups exposed to TMXDI.

The majority of decedent rats exposed lost weight prior to death. The female rat surviving exposure at 0.0533 mg/L failed to gain weight normally during the observation period. The rat of bodyweight gain for rats surviving exposure at 0.02 mg/L was reduced for two days, subsequently gain for this group was similar to that of the control rats.

Males - Mean Body Weight (gm)

	Day of Observation		
	0	7	14
Dose Group			

Control (mg/L)	315	353	384
0.316	311	--	--
0.0935	343	275	--
0.0533	294	--	--
0.0200	309	311	370

Females - Mean Body Weight (gm)

	Day of Observation		
	0	7	14
Dose Group			
Control (mg/L)	220	246	268
0.316	217	--	--
0.0935	218	188	--
0.0533	227	214	217
0.0200	244	254	269

Control male body weight gain averaged a 23.5% increase, while the low dose (Group 6) males gained only 19.7% over the 14-day observation period. Control females body weight gain averaged a 22% increase, while the only surviving female in Group 5 lost 10.3%. The female rats in the low dose (Group 6) gained only 10.2%. All other male and female rats in the mid and high dose groups died prior to day 14.

The lung weight to body weight ratios for the majority of surviving and decedent rats were higher than the control values. The ratios for the surviving test rats at 0.02 mg/L were within normal limits. Abnormalities seen in decedent rats exposed included minimal to marked congestion of the lungs, a swollen appearance of the lungs, a white frothy fluid in the trachea, a fluid-filled thoracic cavity, distension of the gastrointestinal tract with gas, opacities of the eyes and red/brown staining around the snout and jaws. Minimal to moderate congestion of the lungs was the major finding in rats surviving exposure.

Test condition : Each group, containing 5 male and 5 female rats, was exposed continuously for 4 hours to an atmosphere containing droplet aerosol and vapor of TMXDI. The animals were placed in whole-body exposure chambers within a large cabinet. The test atmosphere entered through a port at the base of the chamber and passed out through small holes in the lower edge of the square section. A supply of clean, dried air was connected to the generator and the supply pressure was adjusted to a flow rate of 15 L/min. The total chamber air flow was made up to 25 L/min. Airflow was monitored throughout the exposure using in-line flow meters. The aerosol generator was allowed to equilibrate for 11-minutes followed by a 4-hour period of continuous operation. The generator was then turned off and the animals were removed from the chamber after the chamber was allowed to clear. The exposure levels were obtained by adjusting the rate at which the test article was supplied to the generator. Seven air samples were taken during each exposure and analyzed for TMXDI concentration. Chamber concentrations and particle size distribution were measured analytically. Temperature and relative humidity in the inhalation chambers were monitored. The mean concentrations of droplet aerosol and vapor concentrations tested were Group 1: Control, Group 2: 0.316 mg/L, Group 3: 0.0935 mg/L, Group 5: 0.0533 mg/L, and Group 6: 0.02 mg/L. Group 4 received a large overdose during the last hour due to technical failure. These rats were removed from the study immediately following the exposure period and humanely killed. The particle size distribution as MMAD (micrometers) for the exposure concentrations were 2.7, 2.7, 3.2, and 3.5, resulting in 91, 91, 87, and 80% respirable fractions, respectively.

The rats were observed continuously for clinical signs of reaction to the test substance during exposure and at least twice daily throughout the observation period. The clinical signs w ere recorded at the end of the chamber equilibration period, at 0.25, 0.5 and 1 hour and then at hourly intervals during exposure. During the observation period, the clinical signs were recorded once in the morning and then as necessary following a later check for clinical signs. Body weights were determined daily from the date of receipt of the animals until the end of the obser vation period. All surviving animals were subject to a detailed macroscopic examination. The lungs were removed, dissected clear of surrounding tissue and weighed to calculate lug weight to body weight ratios. The lungs and all macroscopic abnormalities were preserved.

Test substance : Purity of the test material (Lot #348) was 99.3%.

Reliability : (1) valid without restriction
GLP guideline studies are assigned a reliability code of 1a according to the criteria established by Klimisch et al. (Regula tory Toxicology and Pharmacology 25: 1-5, 1997).

27.01.2005 (17)

Type : LC50
Value : = .24 mg/L
Species : guinea pig
Strain : other: English Smooth-Haired (Cavia porcellus)
Sex : male/female
Number of a nimals : 50
Vehicle :
Doses : 0.195, 0.233, 0.355, and 0.457 mg/L
Exposure time : 1 hour(s)
Method : other: Acute Toxicity of Inhaled TMXDI in the Guinea Pig
Year : 1982
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Result : Chamber concentrations tested were 0, 0.195, 0.233, 0.355, and 0.457 mg/L. The count median diameter of the particles ranged from 1.7 to 3.0 micrometers. 0/5, 1/5, 3/5, 5/5, and 5/5 males died and 0/5, 2/5, 2/5, 3/5, and 5/5 females died during the study period. The 1 hour inhalation LC50 = 0.240 (0.190 to 0.303) mg/L.

Clinical signs observed in surviving animals during the first three days post-exposure consisted of weakness, lethargy, gasping/rales, and discharge from eyes, nose or mouth. Body weight losses occurred in all treatment groups. Gross pathology revealed swollen, reddened, rubbery lungs and lung congestion in animals that died. Swelling, reddening, increased consistency, collapse and foci of discoloration were observed at termination in survivors.

Test condition : Each group, containing five male and five female guinea pigs, was exposed once for 1 hour to an aerosol generated from the test article. The animals were placed in the chamber and the aerosol generator was allowed to equilibrate for 10-minutes followed by a 50-minute period of continuous operation. The generator was then turned off and the animals were removed from the chamber after another 10 minutes. The exposure levels were obtained by adjusting the rate at which the test article was supplied to the generator. Nominal chamber calculations were calculated from the weight loss from the generator and the total airflow through the chamber during the 1-hour exposure period. Chamber concentrations and particle size distribution were measured an alytically. Gravimetric chamber concentrations and Gas Chromatograph Analysis were used to analytically determine the test chamber concentrations. Particle size was assessed using a May Cascade Impactor and an optical counting and sizing procedure of Cas ella & Co. Ltd. Temperature and relative humidity in the

inhalation chambers were monitored. Airflow was set at 45L/min. A slight negative pressure within the chamber with respect to room atmosphere was maintained.

Clinical signs were observed for all groups on the day of exposure and twice daily during the 14-day recovery period. Body weights were determined on the day prior to treatment and on days 2, 3, 4, 7 and 14 of the study. All surviving animals were subject to a detailed gross pathology examination.

The LC50 value and the 95% CI were calculated using the method of Litchfield and Wilcoxon, Journal of Pharmacology & Experimental Therapeutics, 1949, 96(2), 99-113. The calculations were based on concentrations of test article measured analytically.

Reliability : (1) valid without restriction
This study is assigned a reliability code of 1b according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997). Comparable to a guideline study.

27.01.2005 (7)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	> 2000 mg/kg bw
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male/female
Number of animals	:	10
Vehicle	:	
Doses	:	2000 mg/kg bw
Method	:	other: Draize test
Year	:	1981
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Result : One death occurred on day 4 but no specific signs of systemic toxicity were observed. Dermal irritation was observed and was maximal 14 days after dosing, with a mean score of 3.9 out of 4. Significant irritation and eschar formation was evident at day 4 and persisted until terminal sacrifice.

Gross port-mortem examination revealed no significant findings related to treatment except for scabbing and eschar formation. There were no remarkable changes in body weights.

Test condition : A single dose of 2000 mg/kg was administered topically to the abraded skin of 10 rabbits (5/sex) and was maintained in contact with the skin for 24 hours with an occlusive wrap. All animals were observed twice daily throughout the study. Body weights were obtained on days-1, 0, 1, 2, 3, 10 and 14. The degree of dermal irritation was scored on days 1, 2, 3, 4, 7 and 14 with the Draize technique (J. Pharmacol. Exp. Therap. 82: 377-390, 1944). Physical examinations were performed on day -1. On day 14 all surviving animals were humanely killed and gross postmortem examinations were performed. Samples of the treated skin were retained.

Test substance : The Batch of material used was S-13708-76.

Reliability : (1) valid without restriction
This study is assigned a reliability code of 1d according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997). Meets generally accepted scientific standards and is described in sufficient detail.

26.01.2005 (4)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	6
Vehicle	:	Dosed as received
PDII	:	
Result	:	moderately irritating
Classification	:	
Method	:	other
Year	:	1981
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : Primary Dermal Irritation Study according to the method described in Federal Register Volume 43, 37336, Part 163.81-5 and Federal Register Volume 44, 44054, Part 772.112-25.

Result : At the 24- and 72-hour evaluations, scores for erythema ranged from very slight to severe for intact sites and from well-defined to severe for abraded sites. Scores for edema ranged from none to slight for both intact and abraded sites. There were no important differences in skin irritation between intact and abraded sites.

Since all animals exhibited skin irritation at 72 hours, gradings continued until day 13. By day 6, all sites in all animals showed eschar formation which persisted, at all but two sites on one animal. The study was terminated at day 13.

Primary Irritation Index = 3.3

Test condition : The study was performed on 6 male rabbits. The test sites were prepared by closely clipping the hair of two sites on the right side of the rabbit's spine and two on the left side. 24 hours after clipping the hair, 2 of the application sites were mechanically abraded. A single 0.5 ml dose of the test article was applied to a 1-inch square gauze patch and applied to each of the 4 test sites (2 abraded and 2 intact) on each animal. The patches were held in place with tape and covered with an occlusive binder. The binder was removed 24 hours later, the test sites were wiped (not washed) to remove remaining test article. Skin reactions were evaluated ~2 hours after wiping.

The animals were observed twice daily and skin reactions were scored at ~24 and 72 hours and daily thereafter until 13 days post-dose.

Reliability : (1) valid without restriction
This study is assigned a reliability code of 1d according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997). Meets generally accepted scientific standards and is described in sufficient detail.

26.01.2005 (11)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	
Dose	:	

Exposure time	:	
Comment	:	
Number of animals	:	9
Vehicle	:	
Result	:	slightly irritating
Classification	:	
Method	:	Draize Test
Year	:	1981
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4

Remark : The study was conducted under the spirit of GLP with a Quality Assurance Compliance Audit Documented.

Result : All rabbits survived and gained weight. Ocular exposure produced no corneal damage at any time in the rabbit's eyes. All treated eyes responded to light and an iridal score was not observed in any rabbits. However, discharge, chemosis and redness of the conjunctivae were observed in all animals with either washed or unwashed eyes. Rinsing the eye with water lessened irritation. Irritation to the conjunctivae appeared to dissipate but still persisted at the termination of the study. The average of the Draize Irritation Scores for 24, 48 and 72 hours was 15.1 and 13.6 on a scale of 110 for the six washed and three unwashed eyes, respectively.

Test condition : The test was conducted according to the method of Draize (J. Pharmacol. Exp. Therap. 82: 377-390, 1944) on female rabbits. A single dose of 100 microliters of undiluted TMXDI was placed in the cupped lower lid of the right eye of each rabbit; the left eye served as an untreated control. One group of six rabbits received no further treatment. A second group of three rabbits had the right eyes rinsed with water for 60 seconds, 30 seconds after instillation of the compound. During the 15 day study, the eyes were examined for discharge, chemosis, inflammation, and opacity on days 1,2,3,4,7,10 and 13 after dosing and Ocular Irritation Scores (Draize Scores) were calculated. The animals were humanely killed without necropsy on day 14.

Test substance : The Batch used was S-13708-76.

Reliability : (1) valid without restriction
This study is assigned a reliability code of 1d according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997). Meets generally accepted scientific standards and is described in sufficient detail.

27.01.2005 (6)

5.3 SENSITIZATION

Type	:	other: Dermal Sensitization Study
Species	:	guinea pig
Number of animals	:	30
Vehicle	:	other: olive oil
Result	:	
Classification	:	
Method	:	other
Year	:	1981
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Result : Four of 10 animals used for the primary skin irritation phase showed some degree of weight loss over the three-day test period. All animals that survived the main study gained weight. During the main study (between challenge and rechallenge), one male challenged with IPDI was found dead. The cause of death could not be determined.

Contact sensitization was evident for both articles at initial challenge (5 days post-induction). Evidence of sensitization for both articles was negligible upon rechallenge (14 days post-induction).

Test condition : Primary Irritation (Range-finding): Prior to initiation of the induction phase, the primary irritation potential was determined. Five animals (male Hartley Albino Guinea Pigs) were each exposed to 5 dilutions (0.10, 0.05, 0.025, 0.0125, 0.00625 and 0.00%) of either test article or positive control substance. Twenty-five microliters of each dilution and the undiluted vehicle were epicutaneously applied to each animal by gentle inunction. No patch was applied. All animals appeared normal except for skin irritation. Two of 5 animals treated with the positive control isophorene diisocyanate (IPDI) exhibited skin reactions. By 48 hrs the reactions were all grade 1 erythemas. All other test sites appeared normal. Three of 5 animals treated with TMXDI exhibited erythema reactions. No skin irrita tion was observed at TMXDI concentrations of 0.0125% or below.

Induction: Based on the result of the irritation phase, the induction phase was initiated. Single applications of 0.36 molar concentrations of TMXDI and IPDI in olive oil were applied to 10 animals each (two sites per animal) in 25 microliter aliquots by gently inunction. No patch was applied.

Challenge: Five days after the single induction application, each animal was exposed to the same concentration of either TMXDI or IPDI. Twenty-five microliters of each dilution and the undiluted vehicle were epicutaneously applied to each animal at previously untreated sites. No patch was applied. At challenge, test sites were not rotated.

Rechallenge: Nine days after the initial challenge, the a nimals were subjected to a rechallenge. Test sites used at rechallenge had not been previously used. IPDI was applied to all animals. TMXDI was applied only to those animals which had been previously challenged with this test article.

Observations: All animals were observed twice daily for clinical signs. Skin condition was evaluated at ~24 and 48 hrs after each application. Initial body weights were obtained prior to primary skin irritation determinations and the induction phase. Terminal body weights were obtained after skin sites were evaluated for animals used to determine the primary skin irritation and 2 days after the last 48-hr evaluation (rechallenge phase).

Gross Necropsy was performed on the animal found dead.

Evidence of a sensitization r esponse was considered to be skin reactions at sites treated with non-irritating concentrations of the test articles or enhanced skin reactions at sites treated with irritating concentrations.

Test substance : The batch of material used was S-13926-25-3A.

Reliability : (1) valid without restriction
This study is assigned a reliability code of 1d according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997). Meets generally accepted scientific standards and is described in sufficient detail.

26.01.2005 (10)

Type : other: Intradermal and Respiratory Sensitization Study
Species : guinea pig
Number of animals : 24
Vehicle :
Result :
Classification :
Method : other
Year : 1984

GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Lethargy and nasal and oral discharge were observed in both treated groups during the induction exposures. Nasal or oral discharge persisted on the days following exposures in 1 animal. There were no other treatment related clinical abnormalities. There were no statistically significant differences in body weight between the treatment animals and controls. None of the animals showed an increase in respiratory rate equal to or greater than the value 36% used as a threshold as evidence of a positive response. There was, therefore, no evidence of sensitization. There were no treatment-related effects revealed in the lung weight data. Intradermal challenge: There was no evidence of sensitization as evidenced by the absence of scores equal to or greater than 2 for erythema.
Test condition	:	Twelve animals (female English smooth-haired guinea pigs) were randomly allocated to each the test and control group and housed individually. Animals were selected from a starting group of 48 based on their intermediate respiratory rates (in the range of 98 to 129 breaths/min). The group size exceeded the number that could be accommodated simultaneously therefore the groups were divided in 3 subgroups each of 4 animals. Induction: Animals were placed in whole body exposure chambers. Airflow through the 150-L chamber was set at 45 L/min and was measured in the exhaust line by means of a ball-type flowmeter. A slight negative pressure within the chamber with respect to the room atmosphere was maintained. Each guinea pig was exposed for 3 hours on study days 1 - 5 to an aerosol of TMXDI at a target concentration of 36 micrograms/L (concentration selected based on results of range-finding study). Aerosols were generated using Pitt No. 1 generators each fitted with an elutriator. The generators were supplied with 4% v/v TMXDI dissolved in dry acetone, from a syringe pump, and dry compressed air. Make-up air not provided by the compressed air line was conditioned room air. Compressed air to operate the atomizer was supplied by a Sihi air compressor and the air was dried in Hankinson's refrigerated air dryers prior to passage through the aerosol generator. Temperature and relative humidity in the exposure chambers were monitored at intervals during the induction exposure by means of sensors located inside the chamber. Challenge: On study days 22, 23 and 26, animals were exposed nose-only to an aerosol of TMXDI/Guinea Pig Serum Albumin (GPSA, Lot#53F-93991) at a target concentration of 0.015-0.020 mg/L for a 20-minute period. The control animals were similarly exposed to GPSA aerosol. Airflow through the 10-L nose-only chamber was set at 17 L/min and was measured in the exhaust line by means of a ball-type flowmeter. A slight negative pressure within the chamber with respect to the room atmosphere was maintained. Aerosols were generated using Pitt No. 1 glass nebulizer without an elutriator. Compressed air to operate the atomizer was supplied by a Sihi air compressor and the air was pre-dried in Hankinson's refrigerated air dryers prior to passage through the aerosol generator. Chamber Concentrations were determined analytically from air sample drawn on study days 1 to 5. Nominal concentrations for study days 1 to 5 were calculated from total weight of test article consumed during each exposure and total airflow through the exposure system. On study days 22,

23, and 26 air sample concentrations were determined gravimetricllly and by calculation. Overall mean for the analyti cally determined concentrations was 26.7 micrograms/L (target was 36 micrograms/L). Challenge exposure chamber concentrations were a little above, but within acceptable limits of the target range.

Particle Size distribution was measured on day 5 of exposure and a separate analysis was performed for the corresponding GPSA complex. Particle size MMD was determined to be 1.6 (2.4 GSD) and 0.8 (2.5 GSD), respectively.

Clinical Signs: All animals were observed during and immediately after exposure and during recovery period on each day of exposure. Each animal was observed daily throughout the study period. Body weights were determined on the day of randomization, on the first day of exposure prior to treatment, and on days 8, 15 and 22 of the study and on the day of necropsy.

Skin Sensitization: On study day 24 the animals were challenged for skin sensitization potential. TMXDI-GPSA was dissolved in saline to give a 0.0333% concentration. GPSA alone in sterile saline was used as the control. Preliminary work indicated that 0.3% TMXDI-GPSA was the highest non-irritating concentration. The animals were intradermally dosed with 100 microliters of test material and control substance at different sites. The intradermal route was selected in order to assess immediate hypersensitivity.

Test substance : Batch S-14536-86-1, Lot#7
Conclusion : Intradermal and respiratory challenges did not elicit any response indicative of sensitization.
Reliability : (1) valid without restriction
This study is assigned a reliability code of 1d according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997). Meets generally accepted scientific standards and is described in sufficient detail.

26.01.2005 (8)

5.4 REPEATED DOSE TOXICITY

Type : Sub-chronic
Species : other: rat and mouse
Sex : male/female
Strain : other: Sprague-Dawley and CD-1
Route of admin. : inhalation
Exposure period : 13 weeks
Frequency of treatm. : 6 hours per day, 5 days per week, for 13 weeks
Post exposure period : 1 week
Doses : 0, 0.4, 0.8, or 1.6 ppm (mean analytical concentrations were 0.31, 0.72, and 1.46 ppm)
Control group : yes, concurrent vehicle
NOAEL : < .4 ppm
LOAEL : = .4 ppm
Method : other: 14-Week Whole-body Inhalation Toxicity Study
Year : 1990
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Remark : 0.4 ppm is equivalent to 4 mg/m3
Result : The cumulative mean analytical exposure concentrations as determined by HPLC were 0.00, 0.31, 0.72 and 1.46 ppm of TMXDI vapor.

Three male rats, 10 male mice, and 11 female mice from the following groups were found dead during the study.

Target Concentration (ppm)	Number of Animals Found Dead During the Study			
	Rats		Mice	
	Male	Female	Male	Female
0 (control)	0	0	0	0
0.4	0	0	1	0
0.8	0	0	2	2
1.6	3	0	7	9

The animals dying on study were found on study the following study days: Male rats (1.6 ppm) Days 15-18; Male mice (0.4 ppm) Day 18, (0.8 ppm) Days 25-66, (1.6 ppm) Days 6-24; Female mice (0.8 ppm) Days 18-27, (1.6 ppm) Days 7-38.

Exposure-related clinical signs were observed in both species of animals. For rats, respiratory difficulties, e.g. gasping, audible respiration, etc, were primarily observed in the 1.6 ppm group with a few animals in the 0.8 ppm group also exhibiting these signs. Reddening of the ears and paws which occurred in all vapor-related groups was most noticeable during exposure and appeared to be concentration related. Reddened ears and paws were still present in some animals on the morning following approximately 18 hours without exposure. Similar signs were observed in mice. Blepharospasm and alopecia were also observed in mice of the 0.8 and 1.6 ppm groups. The alopecia was prominent during the first several weeks of exposure and in some cases resulted in nearly total hair loss. However, the mice did regenerate new hair during the remainder of the study. The overall percent mortality is presented below:

Mortality Summary (%)

		EXPOSURE CONCENTRATION (PPM)			
SPECIES	SEX	0	0.4	0.8	1.6
RAT	M	0	0	0	30
	F	0	0	0	0
MOUSE	M	0	10	20	70*
	F	0	0	20	90*

* - 1.6 ppm mouse exposure terminated after 7 weeks. 1/sex sacrificed and two males held without exposure until 14 weeks

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Effects on body weight gain for both species were generally concentration related, being depressed for the 1.6 ppm group and being sporadically depressed for the 0.8 and 0.4 ppm groups.

Males - Mean Body Weight (gm)

	Week of Observation		
	0	7	14
Dose Group (ppm)			
Control	374	489	553
0.4	378	484	536

0.8	371	466	527
1.6	375	320*	354*

Females - Mean Body Weight (gm)

	Week of Observation		
	0	7	14
Dose Group (ppm)			
Control	221	293	337
0.4	220	277	312
0.8	218	278	312
1.6	220	248*	274*

* - Statistically significant as compared to controls

Many of the hematology and serum chemistry parameters were abnormal for rats of the 1.6 ppm group, probably because of their generally debilitated condition. Changes in hematology, serum chemistry, and urinalysis noted for male or female rats of the 0.4 and 0.8 ppm groups were an increased mean corpuscular volume, increased erythrocyte count, decreased albumin concentration, decreased glucose concentration, and decreased urine volume. No concentration-related changes in hematology, serum chemistry, or urinalysis were observed in mice exposed to 0.4 or 0.8 ppm.

At necropsy, the principal observations for rats of the 1.6 ppm group which either died or were humanely killed at week 14 included a color change of the lungs (congestion) and emphysematous lungs. For mice which died, pulmonary congestion and alopecia were the principal observations. The lung was the only organ for which biologically significant organ weight changes occurred. Absolute and/or relative (to either body or brain weight) lung weight values were increased for rats of the 1.6 ppm group and female mice (not statistically significant) of the 0.8 ppm group. For rats and mice which died on study, histopathologic lesions generally occurred throughout the entire respiratory tract. In the nasal cavity the lesions included necrosis, ulceration, squamous metaplasia, and inflammatory changes; necrosis and inflammatory changes generally occurred in the larynx and trachea; pulmonary changes included congestion, hemorrhage, necrosis, inflammation and in several animals, bronchiolar submucosal fibrosis.

Microscopic Nasal Cavity Incidence Summary
Animals Sacrificed at Week 14

Species: Rat	0 (Control)	0.4 ppm	0.8 ppm	1.6 ppm
Sex: Male/Female				
Total Number Examined	10/10	10/10	10/10	7/10
Examined, Unremarkable	8/10	0/0	0/0	0/0
Rhinitis	2/0	10**/10**	10**/10**	7**/9**
Ulcerative Rhinitis	0/0	0/0	0/0	3/1
Squamous Metaplasia	2/0	10**/10**	10**/10**	7**/9**
Mucus in Nasal Cavity	0/0	2/1	5*/10	6**/7**
Degeneration, Olfactory Epithelium	0/0	0/0	2/0	5**/1

Species: Mouse	0 (Control)	0.4 ppm	0.8 ppm	1.6 ppm
Sex: Male/Female				
Total Number Examined	10/10	9/10	8/8	2/0

Examined, Unremarkable	10/8	0/0	0/0	0/0
Epithelial Degeneration and Necrosis	0/0	7**/0	1/0	0/0
Acidophilic Droplets, Mucosal Epithelium	0/2	9**/10**	8**/8**	1/0
Rhinitis	0/0	7**/9**	8**/8**	2**/0
Mucus Accumulation In Cavity	0/0	1/5*	2/7**	2*/0
Squamous Metaplasia	0/0	0/9**	8**/8**	2**/0
Cytoplasmic Vacuolization	0/0	0/0	0/2	0/0
Necrotic Rhinitis	0/0	0/0	0/1	0/0

* - Significantly Diffe rent From Control Group at 0.05
** - Significantly Different From Control Group at 0.01

In conclusion, mice and rats exposed to vapor TMXDI for up to 13 complete weeks had evidence of toxicity at all exposure concentrations. A no-observable-effect-level was not established for either species, although the incidence, severity, and depth of histologic lesions within the respiratory tract generally decreased with decreasing exposure concentrations. There were no significant lesions noted in reproductive organs that could be attributed to exposure to TMXDI.

Test condition : This study was designed to assess the toxic effects of TMXDI when administered by inhalation as a vapor to groups of rats and mice. During non-exposure periods, water and food were available to the animals ad libitum. Food and water were withheld during exposures. Each group, (10/sex), was exposed for 6 hours per day, five days per week, for thirteen weeks at target concentrations of 0.4, 0.8 and 1.6 ppm. Temperature and relative humidity measurements were generally recorded 12 times per exposure. Cage placement within the exposure chamber was changed weekly in a predetermined manner to compensate for any possible variations in chamber exposure conditions.

Vapor was generated from a metered syringe pump connected to an electrically heated, vertical glass evaporator. Material passed through the evaporator facilitated by heated compressed air. The evaporator temperature was maintained at a specific range to vaporize the material. Gravimetric analysis was conducted to ascertain if any aerosol was being inadvertently generated. There was no indication of aerosol being present. Particle size distribution was measured 3 times during week 1 and once a week thereafter (except week 4). No mass distribution was calculated since there was no indication of aerosol being generated. Exposure levels were monitored 3x per day by HPLC.

During exposure, physical observations for abnormal signs were recorded on a group basis. Preceding and following each exposure observations were recorded individually. Prior to the first exposure and following exposure the eyes of all rats and mice were examined ophthalmically. All animals were weighed prior to first exposure and then once weekly thereafter. Serum chemistry and hematological evaluations were performed on blood from all surviving rats and mice. The following hematologic parameters were measured or calculated: leukocyte count, erythrocyte count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and platelet count. Serum clinical chemistry analyses were performed as follows: glucose, urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, total protein, albumin, globulin, total bilirubin, direct bilirubin, indirect bilirubin, gamma-glutamyl transferase, calcium, phosphorus, sodium, potassium and chloride. Urinalysis was performed on urine of all surviving animals at end of study. The following urinalysis parameters were measured or assessed: volume,

color, turbidity and osmolality. Semiquantitative measurements were made on urine pH, protein, glucose, ketone, bilirubin, blood and urobilinogen. Necropsy and histopathology was performed on all animals on the study. The brain, liver, kidneys, lungs, and adrenal glands from all surviving animals and the testes from all male animals were weighed at necropsy and statistically compared to those of control animals.

The following reproductive tissues were examined at necropsy with lesions as noted.
Female mice: Cervix, vagina, ovaries (0.8 ppm: 2 mm clear cysts, bilateral), vulva, oviduct, ureter, uterus (control: bilateral dilatation/distention), mammary glands
Male mice: Prostate, testes, penis, mammary gland, epididymides, ureter, coagulating gland, seminal vesicle
Female rats: Cervix, vagina, ovaries, vulva, oviduct, ureter, uterus, mammary glands
Male rats: Prostate, testes (control: size decrease, bilateral, ½ of normal), penis, mammary gland, epididymides, ureter, coagulating gland, seminal vesicle.

During non-exposure animals received food and water ad libitum. Room temperature (20 +/- 2 degrees C) was monitored and recorded twice daily. Relative humidity was maintained between 32-72%, monitored and recorded twice daily. During exposure the daily mean chamber temperature and relative humidity ranged from 18.5 to 28.9 degrees C and 24.9-59.1%, respectively.

Test substance : Respirable vapor of TMXDI, CAS# 2778-42-9 (98% Isocyanic acid, m-phenylenediiso-propylidene in acetone), BRRC # 50-483 A to H.

Reliability : (1) valid without restriction
This study is assigned a reliability code of 1d according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997). Meets generally accepted scientific standards and is described in sufficient detail.

Flag : Critical study for SIDS endpoint

27.01.2005 (14)

Type : Sub-acute
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : inhalation
Exposure period : 4 weeks
Frequency of treatm. : 6 hours per day, 5 days per week
Post exposure period :
Doses : 0.5, 1.5 and 5.0 mg/m3
Control group : yes, concurrent vehicle
NOAEL : = 1.5 mg/m³
NOEL : = .38 mg/m³
Method : other: Whole Body Chamber Exposure: 4-Week Inhalation Toxicity Study.
Year : 1988
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Result : Aerosol concentrations: The cumulative mean analytical exposure concentrations as determined by liquid impingers were 0.00, 0.38. 1.5, and 4.4 mg/m3 of TMXDI in acetone, with an average nominal concentrations of 230, 230, 220 and 200 mg/m3 of TMXDI in acetone for the control, low-, mid-, and high-dose groups, respectively. The cumulative mean analytical exposure concentrations of acetone vapor as determined by MIRAN® analysis were 190, 190, 190 and 180 mg/m3 for the vehicle control, low-, mid-, and high-dose groups, respectively. Particle size distribution determinations indicated the test aerosol atmosphere was respirable. The

following table presents the Chamber Monitoring results:

Parameters*	Group I# 0.0 mg/m3	Group II 0.5 mg/m3	Group III 1.5 mg/m3	Group IV 5.0 mg/m3
MMAD, microns	1.3	1.3	0.90	1.5
G.S.D	1.5	1.6	1.5	1.5
% <10 microns	100	100	100	100

* - MMAD = Mass Median Aerodynamic Diameter; G.S.D. = Geometric Standard Deviation of the MMAD.
# - Control group received acetone only

Animal Observations: All animals survived the duration of the study at all concentrations tested. Physical observations indicated evidence during exposure of reduced activity of increasing incidence with increase of exposure for all levels, and occasional evidence of secretory responses during non-exposure periods which were possibly dose-related.

Body weight measurements showed a statistically significant decrease in males exposed to the high level, prior to sacrifice after the last exposure. While no prior body weight measurements showed statistically significant changes, lower body weights were evident for both sexes exposed to the high-dose beginning around Test Day 5-8.

Males - Mean Body Weight (gm)

	Day of Observation			
	1	8	15	29
Dose Group				
Control (mg/m3)	320	352	383	392
0.5	316	349	381	385
1.5	320	351	373	382
5.0	320	343	367	348

Females - Mean Body Weight (gm)

	Day of Observation			
	1	8	15	29
Dose Group				
Control (mg/m3)	220	241	258	259
0.5	220	237	250	247
1.5	217	239	257	257
5.0	219	239	254	244

There were no significant changes or trends relative to hematologic evaluations. Clinical chemistry tests showed no effects except for a slight, but statistically significant increase in serum calcium and phophorous levels of males exposed to the high concentration; female rats showed a similar trend for these parameters but changes were not statistically significant.

Terminal organ weight and organ-to-body weight ratios showed a statistically significant elevation of relative lung weights for females

exposed to the high concentration; absolute lung weights showed a dose-related trend toward elevation but they were not statistically significant. There were no other differences felt to be due to exposure.

Gross portmortem evaluations showed evidence of discolored lungs in one of five males exposed to the low-level, one male and 1 female (out of five each) exposed to the mid-level and four of five males exposed to the high-level. Microscopically, the significant findings were subacute/chronic inflammations of the lungs only in some high-level animals, and the appearance of hyperplastic and metaplastic changes in the bronchi of several high-dose animals which is suggestive of a dose-related effect. These changes were not seen in animals from the control or the two lower exposure levels.

Test condition : This study was designed to assess the toxic effects of TMXDI when administered by inhalation as a respirable aerosol in a vapor solvent (acetone) to groups of rats. Each group, (5/sex/group), was exposed for 6 hours per day, five days per week, for four weeks at target concentrations of 0.5, 1.5 and 5.0 mg/m3. Control animals (5/sex) received a vapor exposure to acetone only. Animals received a total of 22 exposures (2 additional exposures were added due to low exposure concentrations obtained on Days 1 & 2 of exposure). During non-exposure animals received food and water ad libitum. Room temperature (22 3 C) was monitored and recorded twice daily. Relative humidity was maintained between 30-70%, monitored and recorded twice daily. The animal rooms were kept to a 12 hour light/dark cycle.

Aerosol exposure levels were monitored by impingers analyzed by HPLC four times per chamber per day; in addition, vapor levels were monitored by MIRAN® four times per chamber per day. Particle size distribution measurements were made twice each day using a TSI Aerodynamic Particle Sizer.

Physical observations for abnormal signs were made during exposure for all animals. Detailed physical examinations were recorded pretest and before the first and last exposure each week on Test Days 1, 5, 8, 12, 15, 19, 22 and 26; body weight measurements were also obtained just prior to sacrifice on Test Day 29. Just prior to sacrifice, blood samples were obtained for hematology and clinical chemistry, then all animals were sacrificed, selected organs (adrenals, brain, heart, kidneys, liver, lungs, ovaries and testes) were weighed and organ-to-body weight ratios were calculated. Hematology and clinical chemistry parameters evaluated included: hemoglobin concentration, hematocrit, erythrocyte count, clotting time, total and differential leukocyte counts; serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, blood urea nitrogen, creatinine, fasting glucose, total protein, sodium, potassium, chloride calcium and inorganic phosphorus.

Complete gross postmortem examinations were conducted on all animals. All tissues listed as follows were examined microscopically for all control and high-dose animals: adrenals; bone (sternum), bone marrow (sternum), brain (one section of frontal cortex and basal ganglia), esophagus, eyes (2), gonads (2) - ovaries or testes with epididymides, heart, kidneys (2), liver (2 sections from separate lobes), lungs (all lobes and mainstem bronchi), lymph nodes (peribronchial), mammary gland (right inguinal), nasal turbinates (3 sections), pituitary, sciatice nerve, seminal vesicles, spinal cord (cervical), spleen, stomach, thymic region, thyroid/parathyroid, trachea, urinary bladder and uterus.

All the following tissues were examined microscopically for all low- and mid-dose animals (Group II and III): eyes (2), kidney (right), liver (1 section), lungs (2 sections), nasal turbinates (3 sections) and trachea.

During non-exposure animals received food and water ad libitum. Room temperature (22 3 C) was monitored and recorded twice daily. Relative humidity was maintained between 30-70%, monitored and recorded twice daily. The animal rooms were kept to a 12 hour light/dark cycle.

Test substance : Respirable aerosol of TMXDI, CAS# 2778-42-9 (98% Isocyanic acid, m-phenylenediiso-propylidene in acetone), LOT UC-0053.

Reliability : (1) valid without restriction
This study is assigned a reliability code of 1d according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology. 25: 1-5, 1997). Meets generally accepted scientific standards and is described in sufficient detail.

27.01.2005 (13)

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	19 days (males), 40-41 days (females)
Frequency of treatm.	:	daily
Post exposure period	:	
Doses	:	15, 150 and 250 mg/kg bw/day
Control group	:	yes, concurrent vehicle
NOAEL	:	= 150 mg/kg bw
LOAEL	:	= 250 mg/kg bw
Method	:	other: OECD Guide-line 421
Year	:	2005
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Remark : This summary only contains methods and results pertinent to repeated dose toxicity of the parental animals. Reproductive/developmental effects are listed under Sections 5.8.1 and 5.8.2, respectively.

The doses for this study were based on the results of a preliminary fourteen day repeated dose study performed with concentrations up to 1000 mg/kg bw/day. All animals treated with 500 or 1000 mg/kg bw/day were terminated early due to excessive toxicity. All animals exposed to 250 mg/kg bw/day or less survived and did not exhibit signs of excessive toxicity.

The NOAEL for systemic toxicity was 150 mg/kg bw/day. While general irritant type effects were seen at this dose, they were not indicative of systemic toxicity and were not associated with an adverse effect on body weight gain. The one individual with ulcerative change is not considered to be representative of the group.

Result : Mortality and Clinical signs: Thirteen animals were found dead or were killed in extremis during the study (four , five and four treated with 15, 150 and 250 mg/kg bw/day, respectively). All mortalities were considered to be related to mal-administration of the test material.

All animals dosed with 250 and 150 mg/kg bw/day had increased salivation pre dose and up to 1 hour post dose. There were also isolated incidences of increased salivation 5 hours post-dose in these groups. Other clinical findings in 250 mg/kg bw/day group included diarrhea, diuresis, piloerection, hunched posture and tiptoe gait. Piloerection, hunched posture and tiptoe gait were also seen in the 150 mg/kg bw/day group on occasion. Isolated incidences of increased salivation (pre- and post- dose) and tiptoe gait were observed in the 15 mg/kg bw/day group.

Body weight and food consumption: At 250 mg/kg bw/day there was a

slight reduction in body weight gain of males during weeks 2, 4, 5 and 6. Females treated with this dose had lower body weights on Day 0 of gestation and lower body weight gains throughout gestation (which resulted in lower group mean body weights on Days 7, 14 and 20 of gestation). Day 1 and 4 post partum group mean body weights of females treated with 250 mg/kg bw/day were lower than control. The only difference observed in weights or weight gains of animals treated with 150 mg/kg bw/day was a slight decrease in Day 1 post partum body weight. The difference was statistically significant ($p < 0.05$), but was not considered to represent a significant effect as subsequent weight gain and the Day 4 post partum body weight were not significantly different from control. There was no effect of treatment with 15 mg/kg bw/day on body weight.

Food consumption of high dose males was significantly lower than control during the first week of dosing. Food consumption of high dose females was not affected during the maturation period. However, it was decreased during gestation days 1-7, 7-14 and 14-20 and lactation days 1 and 4. There was no effect of treatment with 150 or 15 mg/kg bw/day on food consumption.

Organ weight, gross and histopathology data: There was no effect of treatment on parental organ weight. Both testes and epididymis weights (absolute and relative to body weight) of all treated groups were greater than control. The differences were significant for relative testes ($p < 0.001$) and epididymis weights ($p < 0.05$) of high dose animals. This was due to one control male with small testes (testes weight was 0.209% of body weight compared to others in the group being 0.547 - 0.763% of body weight) and epididymides (epididymis weight was 0.108% of body weight compared to others in the group being 0.205 - 0.284% of body weight) and was not considered to be treatment-related.

All animals found dead or killed in extremis (with the exception of one female at 15 mg/kg bw/day) showed macroscopic changes consistent with dosing trauma, including fluid in the thoracic cavity and fibrous adhesions in thoracic structures. At study termination, there was evidence of gas distension in four high dose males. One mid dose male also had an ulcer in the stomach. There were no significant gross abnormalities in treated females or in males treated with 15 mg/kg bw/day. No treatment-related histopathological changes were observed in the organs that were examined.

Test condition : Date of study: February 3, 2004 - March 19, 2004

Animals: Male and female Sprague-Dawley Crl:CD® (SD)IGS BR rats were obtained from Charles River (UK) Limited, Manston Road, Margate, Kent. They were examined on the day of receipt and acclimated for 7 days. A total of 40 animals/sex were accepted into the study. The males and females weighed 347-387 g and 212-241 g at the start of the study, respectively.

Animals were housed in groups of five by sex in polypropylene cages with stainless steel grid floors and tops, suspended over paper-line polypropylene trays (except during mating and gestation). One male and one female were housed in similar cages during mating. After evidence of successful mating, males were returned to their original cages. The females were then housed individually in cages with solid floors, soft wood chip bedding and stainless steel tops.

Animals were housed in an environmentally-controlled room, under a 12 hour light/dark cycle. The temperature and relative humidity were maintained to operate within a target range of 21 +/- 2 degrees C and 55 +/- 15 %. Air was changed at least 15 times per hour. Certified feed and water were supplied ad libitum. No contaminants were present in food and

water at levels sufficient to affect the outcome of the study.

Test material: The appropriate amount of test material for each group was mixed with arachis oil for 2 minutes to ensure that a homogeneous solution was prepared. Samples of the solution were analyzed for stability and homogeneity prior to the study. The results of the analyses showed that the material was homogeneous in arachis oil and stable for at least 14 days (mean analytical concentrations were 97%, 98% and 90% of nominal 3.75, 37.5 and 62.5 mg/ml solutions after 14 days). Samples of each formulation were taken at the beginning, middle and end of the dosing period and analyzed for concentration of test material. The results of the analyses indicated that the concentrations present were within acceptable limits of the nominal concentrations (mean analytical concentrations were 129%, 102% and 110% of nominal 3.75, 37.5 and 62.5 mg/ml solutions), with the exception that the low dose formulation had a concentration above the acceptable limit on one occasion. The use of this formulation was not considered to influence the outcome of the study.

Study design: The animals were randomly allocated by weight to 4 groups of 10 animals per sex (F0 animals) receiving either 0 (vehicle), 15, 150 or 250 mg/kg/day test material. Animals in each group were uniquely identified. The vehicle (arachis oil) and test material solutions were administered orally by gavage to their respective groups with a plastic dosing catheter attached to a disposable, plastic syringe once daily. The dosing volume was 4 ml/kg. Administration to F0 males and females began 14 days prior to mating and continued through mating. Females continued receiving test material to postnatal day 5.

Following 14 days of dosing, 10 F0 males were randomly paired on a 1:1 basis with 10 F0 females from the same group for up to 14 days. Following positive identification of mating (presence of a copulatory plug in the vagina or the presence of sperm in a vaginal smear following vaginal lavage), the males were returned to their cages. Following mating, all F0 females were allowed to deliver naturally and rear their young to postnatal day 5 (the scheduled day of necropsy).

All F0 animals were observed twice daily for mortality and morbundity (once daily on weekends). Clinical observations were recorded daily. Animals were observed for toxicity at the time of dosing, immediately after dosing and approximately 1 hour after dosing. As a result of clinical signs of a reaction to dosing, animals were also observed 5 hours after dosing from day 8 of the study onwards. Male body weights and food consumption per cage were recorded weekly throughout the study. Body weights and food consumption per cage of females were recorded weekly until mating. After mating, body weights of females were recorded on gestation days 0, 7, 14, and 20 and on lactation days 1 and 4, and food consumption of females was determined for gestation days 1-7, 7-14 and 14-20. Female food consumption also was recorded for the period covering lactation days 1-4.

Males were euthanized after confirmation of successful mating. All surviving adults (including non-fertile animals) and offspring were euthanized on day 5 postpartum. All animals were examined macroscopically for internal and external abnormalities. The testes and epididymides of all adult males were weighed. The coagulating glands, epididymides, prostate, seminal vesicles, testes, pituitary, ovaries, uterus/cervix, and vagina from the high dose and control adult males and females were fixed, processed and examined microscopically by a pathologist.

Statistical evaluations: Data were processed to give litter mean values, group mean values and standard deviations. The food conversion ratio

(group mean weekly body weight gain/ food consumption) was calculated for the premating period. Adult body weight and food consumption, litter size and weight, individual pup body weight, pinna detachment, reproductive and viability indices and organ weight data were analyzed for homogeneity using Bartlett's' test, followed by a one-way analysis of variance (ANOVA). Data that were not homogeneous were subsequently analyzed using a t-test (assuming unequal variances). Dunnett's multiple comparison method was used to analyze data that were homogenous. Relative organ weights were analyzed using the Kruskal-Wallis non parametric rank sum test. Pairwise comparisons were performed using the Mann-Whitney U-test. Histopathological lesions that occurred at an overall frequency of 1 or greater were analyzed using a chi-squared test. Severity grades were analyzed using a Kruskal-Wallis one-way non-parametric ANOVA. Significant differences were reported at the $p < 0.05$, $p < 0.01$ and $p < 0.001$ level (if present).

Test substance : The test material contained > 98% m-teatramethylenexylene diisocyanate (CAS No. 2778-42-9). Impurities were not listed.

Reliability : (2) valid with restrictions
The study is valid without restriction for the reproductive/developmental endpoints. However, some of the parameters measured in guideline repeated dose studies (hematologies, clinical chemistries and complete organ histopathology) were not performed. Therefore, a rating of (2) is appropriate for the repeated dose toxicity endpoint.

27.01.2005 (19)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing : Salmonella typhimurium TA-98, TA-100, TA-1535, TA-1537 and TA-1538
Test concentration : 0.1, 1, 10, 100 ug/plate (0.1 uL test substance/plate)
Cytotoxic concentr. : 100 - 10,000 ug/plate
Metabolic activation : with and without
Result : negative
Method : other: Standard Ames Protocol
Year : 1986
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Result : Results: No evidence of base-pair substitution or frame-shift mutation was seen (see Table).

Strain	Substance	Concentration micrograms/plate	Number of Colonies/Plate Mean w/o S-9	Mean w/ S-9
TA-98	TMXDI	30	41	30
		10	42	25
		3	28	19
		1	19	21
		0.3	12	29
	4-NPD	10	1239	
	2-AA	10		2418
	Acetone	40,000	33	21
TA-100	TMXDI	30	106	S
		10	96	103
		3	114	100
		1	109	118
		0.3	132	101

	NaN3		10	1507	
	2-AA		10		1877
	Acetone		40,000	100	115
TA-1535	TMXDI		30	23	14
			10	24	11
			3	24	9
			1	26	15
			0.3	25	6
		NaN3	10	1686	
		2-AA	10		107
		Acetone	40,000	25	14
TA-1537	TMXDI		30	4	2(T)
			10	5	7
			3	7	9
			1	7	7
			0.3	12	8
		9-AA	60	93	
		2-AA	10		598
		Acetone	40,000	7	8
TA-1538	TMXDI		30	S	16
			10	13	15
			3	4	17
			1	8	15
			0.3	7	16
		4-NPD	10	1267	
		2-AA	10		1112
		Acetone	40,000	5	14

S= Sparse growth of background lawn; counts not included in calculation of mean and standard deviation.
T= Toxic to background lawn.

Test condition : Test article was prepared by mixing TMXDI in acetone to achieve a concentration of 6 mg/ml. Desired test concentrations were obtained by serial dilution. A preliminary toxicity test was performed using TA-100 to determine the level of toxicity of the test substance. Ten doses were tested for toxicity with a plate assay performed in the manner used for mutagenicity determinations. Toxicity was assessed at 24 to 48 hours after treatment by observations for either growth inhibition of the background lawn or a reduction in the number of spontaneous mutants. The maximum concentration tested was 10,000 micrograms/plate. Dose levels ranging from 100 micrograms/plate to 10,000 micrograms/plate were cytotoxic. A dose of 30 micrograms/plate allowed only sparse growth of the background lawn. The lower doses tested (1 - 10 micrograms/plate) did not inhibit growth of the bacteria. Based on these results, 5 doses ranging from 0.3 micrograms/plate to 30 micrograms/plate were selected for the definitive assay. The assay was repeated using TMXDI concentrations of 0.3, 1, 3, 10, and 30 micrograms/plate. The study was performed with and without Aroclor induced rat liver S-9 (50 microliters/plate S-9 preparation). Positive controls were 2-aminoanthracene (2-AA), 4-nitro-o- phenylenediamine (4-NPD), 9-aminoacridine (9-AA), and sodium azide (NaN3). The negative control was the acetone solvent.

Test substance : Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9(In acetone); Purity of test material - ~98%.

Conclusion : Isocyanic acid, m-phenylenediiso-propylidene (TMXDI) was non-mutagenic in the Ames Salmonella Plate Assay with and without metabolic activation

(S-9) using bacterial strains TA-98, TA-100, TA-1535, TA-1537, and TA-1538.

Reliability : (1) valid without restriction
This study is assigned a reliability code of 1d according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997). Meets generally accepted scientific standards and is described in sufficient detail.

Flag : Critical study for SIDS endpoint
26.01.2005 (12)

Type : Chromosomal aberration test
System of testing : Chinese Hamster Ovary (CHO) Cells
Test concentration : 0 - 40 micrograms/ml without S9 and 0 - 40 or 0 - 20 micrograms/ml with S9
Cytotoxic concentr. : > = 20 micrograms/ml
Metabolic activation : with and without
Result : negative
Method : other: OECD Guideline 473 and Method B10 of Commission Directive 2000/32/EC
Year : 2003
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Remark : This study fills the chromosome aberration endpoint.
Result : Preliminary toxicity test: Cytotoxicity was noted at all concentrations in cells incubated for 4 hours with S9 mix and for 24 hours without S9 mix. Cultures containing concentrations > = 152.69 micrograms/ml were discarded due to excessive toxicity. A precipitate was noted in these cultures. The maximum dose levels with metaphases present were 19.1 and 38.17 micrograms/ml for the 4 hour exposures with or without S9, respectively. The maximum concentration with metaphases present in the 24 hour-exposed cultures was 19.1 micrograms/ml. Mitotic index data indicated that approximately 50% growth inhibition was noted at 19.1 micrograms/ml in all three groups. Based on the data, concentrations between 0 - 40 micrograms/ml were chosen for use in the experiments without S9 mix and concentrations between 0 - 40 micrograms/ml and 0 - 20 micrograms/ml were used in the experiments with S9 mix.

Experiment 1: Approximately 52 and 34% cell growth inhibition was noted at 10 micrograms/ml test material without and with S9 mix, respectively. At this concentration, there was 49% and 28% inhibition of the mitotic index (without and with S9 mix, respectively). There were no scorable metaphases at > = 15 micrograms/ml without S9 and > = 20 micrograms/ml in the presence of S9. The dose levels selected for scoring were 2.5, 5 and 10 micrograms/ml in the absence or presence of S9 mix.

There was no effect of test material on the frequency of cells with structural aberrations (ranged from 0-2% in treated vs. 0.5-1.5% in negative control) or polyploidy (ranged from 1-2.9% in treated vs. 0-0.5% in control) at any dose level, in either the presence or absence of S9 mix. The vehicle controls had values within the expected range. Both positive controls induced significant increases ($p < 0.001$) in the frequency of cells with structural aberrations (13,5% and 39.0% for mitomycin C and cyclophosphamide, respectively).

Experiment 2: Approximately 50% cell growth inhibition was noted at 15 micrograms/ml test material in the presence of S9 mix. In the absence of S9 mix, 50% growth inhibition was achieved only at a dose level where there were no metaphases (40 micrograms/ml). In the absence or presence of S9 mix, the maximum concentrations with acceptable toxicity (31% and 35%, respectively) were 15 and 10 micrograms/ml, respectively. The dose levels selected for scoring were 2.5, 5, 10 and 15 micrograms/ml

in the absence of S9 mix and 2.5, 5, and 10 micrograms/ml in the presence of S9 mix.

There was no effect of test material on the frequency of cells with structural aberrations (ranged from 0-1.5% in treated vs. 1.0 -1.5% in negative control) or polyploidy (from 0 -2.4% in treated vs. 0.5% in control) at any dose level, in either the presence or absence of S9 mix. The vehicle controls had values within the expected range. Both positive controls induced significant increases ($p < 0.001$) in the frequency of cells with structural aberrations (43.3% and 87.0% for mitomycin C and cyclophosphamide, respectively).

Test condition : Test materials: The test material was weighed and dissolved in dimethyl sulfoxide (DMSO). The concentration of the stock solution was not given. The highest concentration of material tested was 10 mM. There was no change in pH when the material was added to the culture medium and osmolality was not increased by more than 50 mOsm. Mitomycin C (0.1 or 0.5 micrograms/ml) and cyclophosphamide (5.0 micrograms/ml) were used as the positive controls in the absence and presence of metabolizing enzymes (respectively). Cyclophosphamide was dissolved in DMSO and mitomycin C was dissolved in culture medium before use.

Metabolizing enzymes: S9 was prepared in-house from the livers of male Sprague-Dawley rats weighing approximately 250 g. The animals had received 3 daily, oral doses of a mixture of phenobarbitone (80 mg/kg) and beta naphthoflavone (100 mg/kg) prior to S9 preparation (on day 4). The S9 was stored at -196 degrees C until use.

Cells: The Chinese Hamster Ovary (CHO-WBL) cell line isolated by Kao and Puck (PNAS (USA), 60:1275-1281, 1968) and cloned by O'Neil et al. (Mut. Res. 45:91-101, 1977) was used in the study. Cultures were established at least 16 hours prior to use, grown in McCoys' media (supplemented with L-glutamine, penicillin/streptomycin, amphotericin B and 10% fetal bovine serum), and maintained at 37 degrees C in a humidified atmosphere of 5% CO2 in air.

Preliminary cytotoxicity test: Cells were exposed to 9.5, 19.1, 38.17, 76.34, 152.69, 305.38, 610.75, 1221.5 and 2443 micrograms/ml test material for 4 hours (with and without metabolic activation), followed by a 20-hr recovery period. An additional group of cells was exposed to test material for 24 hours without metabolic activation. Cell growth inhibition was estimated by counting the number of cells at the end of the exposure (or recovery period) with a Coulter counter and expressing the cell count as a percentage of the vehicle control value. Slides were also prepared to determine the number and quality of cells in metaphase and mitotic index. Presence or absence of a precipitate was noted.

Aberration Assay: Two separate experiments were performed. Experiment 1 included cultures exposed to test material with and without S9 mix for 4 hours, followed by 20 hours of culture in treatment-free media. Experiment 2 included cultures exposed to test material and S9 mix for 4 hours, followed by 20 hours of culture in treatment-free medium, plus cultures exposed to test material without S9 mix for 24 hours. In both experiments, the cultures were exposed to at least 3 doses of test material, vehicle and positive controls in duplicate.

Mitosis was arrested by the addition of demecolcine (0.1 micrograms/ml) two hours before cell harvest. At harvest, the cells were trypsinized and suspended in culture medium. A sample of each cell suspension was counted to measure growth inhibition at each concentration. The cells were centrifuged and the culture medium was drawn off and discarded. The cells were then resuspended in 0.075 M hypotonic KCl for a total of 12 minutes (including centrifugation). After centrifugation, most of the

hypotonic solution was drawn off and discarded. The cells were then resuspended in the remaining KCl solution, and fixed by dropping the suspension into fresh methanol/glacial acetic acid (3:1 v/v). The fixative was changed at least 3 times and the cells stored at 4 degrees C for at least 4 hours to ensure fixation.

The cells were resuspended in fresh fixative (if necessary) before centrifugation and resuspension in fixative. Several drops of this suspension were dropped onto clean, wet, labeled microscope slides and left to air dry. Dry slides were stained in Giemsa for 5 minutes, rinsed, dried and mounted. The slides were checked microscopically to determine the quality of the metaphases, toxicity of the material, and presence of a precipitate. The data were used to select dose levels for mitotic index evaluation.

Evaluation: A total of 1000 cells were counted and the number of cells in metaphases recorded. The data were expressed as the mitotic index and as a percentage of the vehicle control value. Where possible, the first 100 consecutive, well-spread metaphases from each culture were counted. Where there were approximately 50% cells with aberrations, slide evaluation was terminated at 50 cells. If the cell had 19-23 chromosomes (was diploid), any gaps, breaks or rearrangements were noted according to the system of Savage (J. Med. Genet. 13:103-122, 1976). If the cell had more than 32 chromosomes it was recorded as polyploidy. Aberrations in these cells were not recorded. Endoreduplicated cells were counted as polyploid. Aberrations were checked by a senior cytogeneticist prior to decoding.

A positive response was recorded if the percentage of diploid cells with aberrations (excluding gaps) exceeded the maximum historical value. A +/- response was recorded if gaps had to be included. Positive responses were also recorded if the percentage of cells with aberrations (excluding gaps) was greater than twice the concurrent control level and there was a dose-response. Data were also analyzed statistically by an unlisted method.

Test substance : The test material (batch UC1081701) contained > 98.1% benzene, 1,3-bis(1-isocyanato-1-methylethyl)-. Impurities were not listed.

Reliability : (1) valid without restriction
GLP guideline studies are assigned a reliability code of 1a according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997).

Flag : Critical study for SIDS endpoint
26.01.2005 (18)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

Type : other: combined reproductive/developmental toxicity screening test
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period :
Frequency of treatm. : daily

Premating exposure period

Male	:	14 days
Female	:	14 days
Duration of test	:	to postpartum day 5
No. of generation studies	:	1
Doses	:	15, 150 and 250 mg/kg bw/day
Control group	:	yes, concurrent vehicle
NOAEL parental	:	= 150 mg/kg bw
NOAEL F1 offspring	:	= 250 mg/kg bw
other: NOAEL reproduction	:	= 250 mg/kg bw
Result	:	The material is not a reproductive toxicant at the doses tested.
Method	:	OECD Guide-line 421
Year	:	2005
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Remark : The doses for this study were based on the results of a preliminary fourteen day repeated dose study performed with concentrations up to 1000 mg/kg bw/day. All animals treated with 500 or 1000 mg/kg bw/day were terminated early due to excessive toxicity. All animals exposed to 250 mg/kg bw/day or less survived and did not exhibit signs of excessive toxicity.

The NOAEL for systemic toxicity in the reproductive/ developmental study was 150 mg/kg bw/day. While general irritant type effects were seen at this dose, they were not indicative of systemic toxicity and were not associated with an adverse effect on body weight gain. The one individual with ulcerative change is not considered to be representative of the group.

Result : Mortality and Clinical signs: Thirteen animals were found dead or were killed in extremis during the study (four, five and four treated with 15, 150 and 250 mg/kg bw/day, respectively). All mortalities were considered to be related to mal-administration of the test material.

All animals dosed with 250 and 150 mg/kg bw/day had increased salivation pre dose and up to 1 hour post dose. There were also isolated incidences of increased salivation 5 hours post-dose in these groups. Other clinical findings in 250 mg/kg bw/day group included diarrhea, diuresis, piloerection, hunched posture and tiptoe gait. Piloerection, hunched posture and tiptoe gait were also seen in the 150 mg/kg bw/day group on occasion. Isolated incidences of increased salivation (pre- and post- dose) and tiptoe gait were observed in the 15 mg/kg bw/day group.

Body weight and food consumption: At 250 mg/kg bw/day there was a slight reduction in body weight gain of males during weeks 2, 4, 5 and 6. Females treated with this dose had lower body weights on Day 0 of gestation and lower body weight gains throughout gestation (which resulted in lower group mean body weights on Days 7, 14 and 20 of gestation). Day 1 and 4 post partum group mean body weights of females treated with 250 mg/kg bw/day were lower than control. The only difference observed in weights or weight gains of animals treated with 150 mg/kg bw/day was a slight decrease in Day 1 post partum body weight. The difference was statistically significant ($p < 0.05$), but was not considered to represent a significant effect as subsequent weight gain and the Day 4 post partum body weight were not significantly different from control. There was no effect of treatment with 15 mg/kg bw/day on body weight.

Food consumption of high dose males was significantly lower than control during the first week of dosing. Food consumption of high dose females was not affected during the maturation period. However, it was decreased during gestation days 1-7, 7-14 and 14-20 and lactation days 1 and 4.

There was no effect of treatment with 150 or 15 mg/kg bw/day on food consumption.

Fertility: There was no effect of treatment on fertility or mating performance. Male and female fertility indices were 100% in the low and mid dose groups and 90% in the high dose group. One high dose and one control pair failed to mate. There was no effect of treatment on pre-coital interval or gestation or parturition length. All pre-coital intervals were < = 5 days. The length of gestation in all animals was 21-22 days. The parturition index was 100% in all groups. There was no significant effect of treatment on the number of implantation sites (ranged from 15 +/- 1 in high dose group to 16 +/- 2 or 3 in all other groups), number of corpora lutea (ranged from 16 +/- 3 or 1 in low and high dose groups, respectively to 17 +/- 2 in control and mid dose groups), pre-implantation loss (ranged from 1.4 +/- 4.2% in low dose group to 7.2 +/- 5.3% in control) or post implantation loss (ranged from 4.0 +/- 6.8 in control to 8.2 +/- 6.0% in low dose group).

Organ weight, gross and histopathology data: There was no effect of treatment on parental organ weight. Both testes and epididymis weights (absolute and relative to body weight) of all treated groups were greater than control. The differences were significant for relative testes ($p < 0.001$) and epididymis weights ($p < 0.05$) of high dose animals. This was due to one control male with small testes (testes weight was 0.209% of body weight compared to others in the group being 0.547 - 0.763% of body weight) and epididymides (epididymis weight was 0.108% of body weight compared to others in the group being 0.205 - 0.284% of body weight) and was not considered to be treatment-related.

All animals found dead or killed in extremis (with the exception of one female at 15 mg/kg bw/day) showed macroscopic changes consistent with dosing trauma, including fluid in the thoracic cavity and fibrous adhesions in thoracic structures. At study termination, there was evidence of gas distension in four males. One mid dose male also had an ulcer in the stomach. There were no significant gross abnormalities in treated females or in males treated with 150 mg/kg bw/day. No treatment-related histopathological changes were observed in the organs that were examined.

Offspring data: There were no significant effects of treatment on live birth or viability index (ranged from 91.9% in high dose to 99.3% in control and from 87.9% in high dose to 100% in mid and low dose, respectively), litter size (ranged from 14.1 +/- 2.0 in high dose to 15.6 +/- 1.5 in low dose at birth and ranged from 13.2 +/- 1.2 in high dose to 15.0 +/- 1.0 in mid dose at post parturm day 5), pinna unfolding, surface righting reflex or sex ratio. There were no significant treatment-related gross abnormalities in offspring at termination.

In the high dose group, there was a significantly lower mean pup weight on Days 1 ($p < 0.001$) and 4 ($p < 0.05$) of lactation. There was a concomitant reduction in mean total litter weight ($p < 0.01$) compared to control values. Offspring weights of high dose animals (average weight was 5.6 +/- 0.8 g on day 1 post partum) were also lower than historical control values (range from 4 studies was 6.2 - 6.9 g on day 1 post partum). However, study control weight values were generally higher than historical controls (average weight was 7.0 +/- 0.6 g on day 1 postpartum). This was due to one control litter with higher than normal mean offspring weight (134.4 g on day 1 postpartum vs. 86.7 - 111.9 g for other control litters). There was no effect of treatment with 150 or 15 mg/kg bw/day on pup body weight.

Test condition : Date of study: February 3, 2004 - March 19, 2004

Animals: Male and female Sprague-Dawley Crl:CD® (SD)IGS BR rats were obtained from Charles River (UK) Limited, Manston Road, Margate, Kent.

They were examined on the day of receipt and acclimated for 7 days. A total of 40 animals/sex were accepted into the study. The males and females weighed 347-387 g and 212-241 g at the start of the study, respectively.

Animals were housed in groups of five by sex in polypropylene cages with stainless steel grid floors and tops, suspended over paper-line polypropylene trays (except during mating and gestation). One male and one female were housed in similar cages during mating. After evidence of successful mating, males were returned to their original cages. The females were then housed individually in cages with solid floors, soft wood chip bedding and stainless steel tops.

Animals were housed in an environmentally-controlled room, under a 12 hour light/dark cycle. The temperature and relative humidity were maintained to operate within a target range of 21 +/- 2 degrees C and 55 +/- 15 %. Air was changed at least 15 times per hour. Certified feed and water were supplied ad libitum. No contaminants were present in food and water at levels sufficient to affect the outcome of the study.

Test material: The appropriate amount of test material for each group was mixed with arachis oil for 2 minutes to ensure that a homogeneous solution was prepared. Samples of the solution were analyzed for stability and homogeneity prior to the study. The results of the analyses showed that the material was homogeneous in arachis oil and stable for at least 14 days (mean analytical concentrations were 97%, 98% and 90% of nominal 3.75, 37.5 and 62.5 mg/ml solutions after 14 days). Samples of each formulation were taken at the beginning, middle and end of the dosing period and analyzed for concentration of test material. The results of the analyses indicated that the concentrations present were within acceptable limits of the nominal concentrations (mean analytical concentrations were 129%, 102% and 110% of nominal 3.75, 37.5 and 62.5 mg/ml solutions), with the exception that the low dose formulation had a concentration above the acceptable limit on one occasion. The use of this formulation was not considered to influence the outcome of the study.

Study design: The animals were randomly allocated by weight to 4 groups of 10 animals per sex (F0 animals) receiving either 0 (vehicle), 15, 150 or 250 mg/kg/day test material. Animals in each group were uniquely identified. The vehicle (arachis oil) and test material solutions were administered orally by gavage to their respective groups with a plastic dosing catheter attached to a disposable, plastic syringe once daily. The dosing volume was 4 ml/kg. Administration to F0 males and females began 14 days prior to mating and continued through mating. Females continued receiving test material to postnatal day 5.

Following 14 days of dosing, 10 F0 males were randomlypaired on a 1:1 basis with 10 F0 females from the same group for up to 14 days. Following positive identification of mating (presence of a copulatory plug in the vagina or the presence of sperm in a vaginal smear following vaginal lavage), the males were returned to their cages. Following mating, all F0 females were allowed to deliver naturally and rear their young to postnatal day 5 (the scheduled day of necropsy). During the period of expected parturition, the females were observed three times daily for parturition (twice on weekends). The date of mating, date and time of start and completion of parturition and duration of gestation were recorded for each female. After parturition was complete, the number of live and dead offspring was recorded. The following were recorded for each litter: number of pups born, number and sex of pups alive from days 1 to 4 postpartum, clinical condition of pups from birth to day 4 post partum and individual litter weights on days 1 and 4 postpartum. All live offspring were observed for surface righting reflex on day 1 post partum and detachment of pinna.

All F0 animals were observed twice daily for mortality and morbundity (once daily on weekends). Clinical observations were recorded daily. Animals were observed for toxicity at the time of dosing, immediately after dosing and approximately 1 hour after dosing. As a result of clinical signs of a reaction to dosing, animals were also observed 5 hours after dosing from day 8 of the study onwards. Male body weights and food consumption per cage were recorded weekly throughout the study. Body weights and food consumption per cage of females were recorded weekly until mating. After mating, body weights of females were recorded on gestation days 0, 7, 14, and 20 and on lactation days 1 and 4, and food consumption of females was determined for gestation days 1-7, 7-14 and 14-20. Female food consumption also was recorded for the period covering lactation days 1-4.

Males were euthanized after confirmation of successful mating. All surviving adults (including non-fertile animals) and offspring were euthanized on day 5 postpartum. All animals were examined microscopically for internal and external abnormalities. The numbers of corpora lutea and uterine implantation sites in pregnant females were counted. The uteri of apparently nonpregnant females were examined. The testes and epididymides of all adult males were weighed. The coagulating glands, epididymides, prostate, seminal vesicles, testes, pituitary, ovaries, uterus/cervix, and vagina from the high dose and control adult males and females were fixed, processed and examined microscopically by a pathologist.

Statistical evaluations: Data were processed to give litter mean values, group mean values and standard deviations. The food conversion ratio (group mean weekly body weight gain/ food consumption) was calculated for the premating period. The pre coital interval (time between initial pairing and evidence of mating), mating index, pregnancy index, gestation length, parturition index, live birth index, viability index and sex ratio were determined. A continuity correction of a half day was subtracted from the age of appearance of pinna detachment for those litters born overnight. Adult body weight and food consumption, litter size and weight, individual pup body weight, pinna detachment, reproductive and viability indices and organ weight data were analyzed for homogeneity using Bartlett's' test, followed by a one-way analysis of variance (ANOVA). Data that were not homogeneous were subsequently analyzed using a t-test (assuming unequal variances). Dunnett's multiple comparison method was used to analyze data that were homogenous. Individual pre-coital intervals, gestation length, offspring reflexological responses, sex ratios and relative organ weights were analyzed using the Kruskal-Wallis non parametric rank sum test. Pairwise comparisons were performed using the Mann-Whitney U-test. Histopathological lesions that occurred at an overall frequency of 1 or greater were analyzed using a chi-squared test. Severity grades were analyzed using a Kruskal-Wallis one-way non-parametric ANOVA. Significant differences were reported at the $p < 0.05$, $p < 0.01$ and $p < 0.001$ level (if present).

Test substance : The test material contained > 98% m-teatramethylenexylene diisocyanate (CAS No. 2778-42-9). Impurities were not listed.

Reliability : (1) valid without restriction
GLP guideline studies are assigned a reliability code of 1a according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997).

Flag : Critical study for SIDS endpoint
27.01.2005 (19)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	
Frequency of treatm.	:	daily
Duration of test	:	14 days prior to mating to lactation day 5
Doses	:	15, 150 and 250 mg/kg bw/day
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	= 150 ml/kg bw
NOAEL teratogen.	:	= 250 mg/kg bw
other: NOAEL developmental	:	= 250 mg/kg bw
Result	:	The material is not a developmental toxicant at the doses tested.
Method	:	other: OECD Guideline 421
Year	:	2005
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Remark : From this point forward, this summary is identical to the summary listed above under Section 5.8.1 (Toxicity to Fertility).

The doses for this study were based on the results of a preliminary fourteen day repeated dose study performed with concentrations up to 1000 mg/kg bw/day. All animals treated with 500 or 1000 mg/kg bw/day were terminated early due to excessive toxicity. All animals exposed to 250 mg/kg bw/day or less survived and did not exhibit signs of excessive toxicity.

The NOAEL for systemic toxicity in the reproductive/ developmental study was 150 mg/kg bw/day. While general irritant type effects were seen at this dose, they were n ot indicative of systemic toxicity and were not associated with an adverse effect on body weight gain. The one individual with ulcerative change is not considered to be representative of the group.

Result : Mortality and Clinical signs: Thirteen animals were found dead or were killed in extremis during the study (four, five and four tre ated with 250, 150 and 150 mg/kg bw/day, respectively). All mortalities were considered to be related to mal-administration of the test material.

All animals dosed with 250 and 150 mg/kg bw/day had increased salivation pre dose and up to 1 hour post dose. There were also isolated incidences of increased salivation 5 hours post-dose in these groups. Other clinical findings in 250 mg/kg bw/day group included diarrhea, diuresis, piloerection, hunched posture and tiptoe gait. Piloerection, hunched posture and tiptoe gait were also seen in the 150 mg/kg bw/day group on occasion. Isolated incidences of increased salivation (pre- and post- dose) and tiptoe gait were observed in the 15 mg/kg bw/day group.

Body weight and food consumption: At 250 mg/kg bw/day there was a slight reduction in body weight gain of males during weeks 2, 4, 5 and 6. Females treated with this dose had lower body weights on Day 0 of gestation and lower body weight gains throughout gestation (which resulted in lower group mean body weights on Days 7, 14 and 20 of gestation). Day 1 and 4 post partum group mean body weights of females treated with 250 mg/kg bw/day were lower than control. The only difference observed in weights or weight gains of animals treated with 150 mg/kg bw/day was a slight decrease in Day 1 post partum body weight. The difference was statistically significant ($p < 0.05$) , but was not considered to represent a significant effect as subsequent weight gain and the Day 4 post partum

body weight were not significantly different from control. There was no effect of treatment with 15 mg/kg bw/day on body weight.

Food consumption of high dose males was significantly lower than control during the first week of dosing. Food consumption of high dose females was not affected during the maturation period. However, it was decreased during gestation days 1-7, 7-14 and 14-20 and lactation days 1 and 4. There was no effect of treatment with 150 or 15 mg/kg bw/day on food consumption.

Fertility: There was no effect of treatment on fertility or mating performance. Male and female fertility indices were 100% in the low and mid dose groups and 90% in the high dose group. One high dose and one control pair failed to mate. There was no effect of treatment on pre-coital interval or gestation or parturition length. All pre-coital intervals were < = 5 days. The length of gestation in all animals was 21-22 days. The parturition index was 100% in all groups. There was no significant effect of treatment on the number of implantation sites (ranged from 15 +/- 1 in high dose group to 16 +/- 2 or 3 in all other groups), number of corpora lutea (ranged from 16 +/- 3 or 1 in low and high dose groups, respectively to 17 +/- 2 in control and mid dose groups), pre-implantation loss (ranged from 1.4 +/- 4.2% in low dose group to 7.2 +/- 5.3% in control) or post implantation loss (ranged from 4.0 +/- 6.8 in control to 8.2 +/- 6.0% in low dose group).

Organ weight, gross and histopathology data: There was no effect of treatment on parental organ weight. Both testes and epididymis weights (absolute and relative to body weight) of all treated groups were greater than control. The differences were significant for relative testes ($p < 0.001$) and epididymis weights ($p < 0.05$) of high dose animals. This was due to one control male with small testes (testes weight was 0.209% of body weight compared to others in the group being 0.547 - 0.763% of body weight) and epididymides (epididymis weight was 0.108% of body weight compared to others in the groupbeing 0.205 - 0.284% of body weight) and was not considered to be treatment-related.

All animals found dead or killed in extremis (with the exception of one female at 15 mg/kg bw/day) showed macroscopic changes consistent with dosing trauma, including fluid in the thoracic cavity and fibrous adhesions in thoracic structures. At study termination, there was evidence of gas distension in four males. One mid dose male also had an ulcer in the stomach. There were no significant gross abnormalities in treated females or in males treated with 150 mg/kg bw/day. No treatment-related histopathological changes were observed in the organs that were examined.

Offspring data: There were no significant effects of treatment on live birth or viability index (ranged from 91.9% in high dose to 99.3% in control and from 87.9% in high dose to 100% in mid and low dose, respectively), litter size (ranged from 14.1 +/- 2.0 in high dose to 15.6 +/- 1.5 in low dose at birth and ranged from 13.2 +/- 1.2 in high dose to 15.0 +/- 1.0 in mid dose at post parturm day 5), pinna unfolding, surface righting reflex or sex ratio. There were no significant treatment-related gross abnormalities in offspring at termination.

In the high dose group, there was a significantly lower mean pup weight on Days 1 ($p < 0.001$) and 4 ($p < 0.05$) of lactation. There was a concomitant reduction in mean total litter weight ($p < 0.01$) compared to control values. Offspring weights of high dose animals (average weight was 5.6 +/- 0.8 g on day 1 post partum) were also lower than historical control values (range from 4 studies was 6.2 - 6.9 g on day 1 post partum). However, study control weight values were generally higher than historical controls (average weight was 7.0 +/- 0.6 g on day 1 postpartum). This was due to

one control litter with higher than normal mean offspring weight (134.4 g on day 1 postpartum vs. 86.7 - 111.9 g for other control litters). There was no effect of treatment with 150 or 15 mg/kg bw/day on pup body weight.

Test condition : Date of study: February 3, 2004 - March 19, 2004

Animals: Male and female Sprague-Dawley Crl:CD® (SD)IGS BR rats were obtained from Charles River (UK) Limited, Manston Road, Margate, Kent. They were examined on the day of receipt and acclimated for 7 days. A total of 40 animals/sex were accepted into the study. The males and females weighed 347-387 g and 212-241 g at the start of the study, respectively.

Animals were housed in groups of five by sex in polypropylene cages with stainless steel grid floors and tops, suspended over paper-line polypropylene trays (except during mating and gestation). One male and one female were housed in similar cages during mating. After evidence of successful mating, males were returned to their original cages. The females were then housed individually in cages with solid floors, soft wood chip bedding and stainless steel tops.

Animals were housed in an environmentally-controlled room, under a 12 hour light/dark cycle. The temperature and relative humidity were maintained to operate within a target range of 21 +/- 2 degrees C and 55 +/- 15 %. Air was changed at least 15 times per hour. Certified feed and water were supplied ad libitum. No contaminants were present in food and water at levels sufficient to affect the outcome of the study.

Test material: The appropriate amount of test material for each group was mixed with arachis oil for 2 minutes to ensure that a homogeneous solution was prepared. Samples of the solution were analyzed for stability and homogeneity prior to the study. The results of the analyses showed that the material was homogeneous in arachis oil and stable for at least 14 days (mean analytical concentrations were 97%, 98% and 90% of nominal 3.75, 37.5 and 62.5 mg/ml solutions after 14 days). Samples of each formulation were taken at the beginning, middle and end of the dosing period and analyzed for concentration of test material. The results of the analyses indicated that the concentrations present were within acceptable limits of the nominal concentrations (mean analytical concentrations were 129%, 102% and 110% of nominal 3.75, 37.5 and 62.5 mg/ml solutions), with the exception that the low dose formulation had a concentration above the acceptable limit on one occasion. The use of this formulation was not considered to influence the outcome of the study.

Study design: The animals were randomly allocated by weight to 4 groups of 10 animals per sex (F0 animals) receiving either 0 (vehicle), 15, 150 or 250 mg/kg/day test material. Animals in each group were uniquely identified. The vehicle (arachis oil) and test material solutions were administered orally by gavage to their respective groups with a plastic dosing catheter attached to a disposable, plastic syringe once daily. The dosing volume was 4 ml/kg. Administration to F0 males and females began 14 days prior to mating and continued through mating. Females continued receiving test material to postnatal day 5.

Following 14 days of dosing, 10 F0 males were randomly paired on a 1:1 basis with 10 F0 females from the same group for up to 14 days. Following positive identification of mating (presence of a copulatory plug in the vagina or the presence of sperm in a vaginal smear following vaginal lavage), the males were returned to their cages. Following mating, all F0 females were allowed to deliver naturally and rear their young to postnatal day 5 (the scheduled day of necropsy). During the period of expected parturition, the females were observed three times daily for parturition (twice on weekends). The date of mating, date and time of start and completion of

parturition and duration of gestation were recorded for each female. After parturition was complete, the number of live and dead offspring was recorded. The following were recorded for each litter: number of pups born, number and sex of pups alive from days 1 to 4 postpartum, clinical condition of pups from birth to day 4 post partum and individual litter weights on days 1 and 4 postpartum. All live offspring were observed for surface righting reflex on day 1 post partum and detachment of pinna.

All F0 animals were observed twice daily for mortality and morbundity (once daily on weekends). Clinical observations were recorded daily. Animals were observed for toxicity at the time of dosing, immediately after dosing and approximately 1 hour after dosing. As a result of clinical signs of a reaction to dosing, animals were also observed 5 hours after dosing from day 8 of the study onwards. Male body weights and food consumption per cage were recorded weekly throughout the study. Body weights and food consumption per cage of females were recorded weekly until mating. After mating, body weights of females were recorded on gestation days 0, 7, 14, and 20 and on lactation days 1 and 4, and food consumption of females was determined for gestation days 1-7, 7-14 and 14-20. Female food consumption also was recorded for the period covering lactation days 1-4.

Males were euthanized after confirmation of successful mating. All surviving adults (including non-fertile animals) and offspring were euthanized on day 5 postpartum. All animals were examined microscopically for internal and external abnormalities. The numbers of corpora lutea and uterine implantation sites in pregnant females were counted. The uteri of apparently nonpregnant females were examined. The testes and epididymides of all adult males were weighed. The coagulating glands, epididymides, prostate, seminal vesicles, testes, pituitary, ovaries, uterus/cervix, and vagina from the high dose and control adult males and females were fixed, processed and examined microscopically by a pathologist.

Statistical evaluations: Data were processed to give litter mean values, group mean values and standard deviations. The food conversion ratio (group mean weekly body weight gain/ food consumption) was calculated for the premating period. The pre coital interval (time between initial pairing and evidence of mating), mating index, pregnancy index, gestation length, parturition index, live birth index, viability index and sex ratio were determined. A continuity correction of a half day was subtracted from the age of appearance of pinna detachment for those litters born overnight. Adult body weight and food consumption, litter size and weight, individual pup body weight, pinna detachment, reproductive and viability indices and organ weight data were analyzed for homogeneity using Bartlett's' test, followed by a one-way analysis of variance (ANOVA). Data that were not homogeneous were subsequently analyzed using a t-test (assuming unequal variances). Dunnett's multiple comparison method was used to analyze data that were homogenous. Individual pre-coital intervals, gestation length, offspring reflexological responses, sex ratios and relative organ weights were analyzed using the Kruskal-Wallis non parametric rank sum test. Pairwise comparisons were performed using the Mann-Whitney U-test. Histopathological lesions that occurred at an overall frequency of 1 or greater were analyzed using a chi-squared test. Severity grades were analyzed using a Kruskal-Wallis one-way non-parametric ANOVA. Significant differences were reported at the $p < 0.05$, $p < 0.01$ and $p < 0.001$ level (if present).

Test substance : The test material contained > 98% m-teatramethylenexylene diisocyanate (CAS No. 2778-42-9). Impurities were not listed.

Reliability : (1) valid without restriction
GLP guideline studies are assigned a reliability code of 1a according to the criteria established by Klimisch et al. (Regulatory Toxicology and

Pharmacology 25: 1-5, 1997).

Flag : Critical study for SIDS endpoint
27.01.2005 (19)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

Type : other: investigation of reproductive organs from 14 week study
In vitro/in vivo : In vivo
Species : other: rat and mouse
Sex : male/female
Strain : other: Sprague-Dawley and CD-1
Route of admin. : inhalation
Exposure period : 13 weeks
Frequency of treatm. : 6 hours per day, 5 days per week, for 13 weeks
Duration of test : 14 weeks
Doses : 0, 0.4, 0.8, or 1.6 ppm (mean analytical concentrations were 0.31, 0.72, and 1.46 ppm)
Control group : yes, concurrent vehicle
Result : test material is not a reproductive toxicant
Method : other: 14-Week Whole-body Inhalation Toxicity Study
Year : 1990
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Remark : Based on the results of the 90-day repeat dose inhalation study there were no macro or microscopic changes in any of the male or female reproductive organs that could be attributed to exposure to TMXDI. Thus suggestive that at the doses tested the material would not be a reproductive toxicant. Based on this it is estimated that this material would not be a reproductive toxicant.

Result :

The cumulative mean analytical exposure concentrations as determined by HPLC were 0.00, 0.31, 0.72 and 1.46 ppm of TMXDI vapor.

Three male rats, 10 male mice, and 11 female mice from the following groups were found dead during the study.

Target Concentration (ppm)	Number of Animals Found Dead During the Study			
	Rats		Mice	
	Male	Female	Male	Female
0 (control)	0	0	0	0
0.4	0	0	1	0
0.8	0	0	2	2
1.6	3	0	7	9

The animals dying on study were found on study the following study days: Male rats (1.6 ppm) Days 15-18; Male mice (0.4 ppm) Day 18, (0.8 ppm) Days 25-66, (1.6 ppm) Days 6-24; Female mice (0.8 ppm) Days 18-27, (1.6 ppm) Days 7-38.

Exposure-related clinical signs were observed in both species of animals. For rats, respiratory difficulties, e.g. gasping, audible respiration, etc, were primarily observed in the 1.6 ppm group with a few animals in the 0.8 ppm group also exhibiting these signs. Reddening of the ears and paws which occurred in all vapor-related groups was most noticeable during exposure and appeared to be concentration related. Reddened ears and paws were still present in some animals on the morning following approximately 18 hours without exposure. Similar signs were observed in mice. Blepharospasm and alopecia were also observed in mice of the 0.8 and 1.6

ppm groups. The alopecia was prominent during the first several weeks of exposure and in some cases resulted in nearly total hair loss. However, the mice did regenerate new hair during the remainder of the study. The overall percent mortality is presented below:

Mortality Summary (%)

		EXPOSURE CONCENTRATION (PPM)			
SPECIES	SEX	0	0.4	0.8	1.6
RAT	M	0	0	0	30
	F	0	0	0	0
MOUSE	M	0	10	20	70*
	F	0	0	20	90*

* - 1.6 ppm mouse exposure terminated after 7 weeks. 1/sex sacrificed and two males held without exposure until 14 weeks

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Effects on body weight gain for both species were generally concentration related, being depressed for the 1.6 ppm group and being sporadically depressed for the 0.8 and 0.4 ppm groups.

Males - Mean Body Weight (gm)

	Week of Observation		
	0	7	14
Dose Group (ppm)			
Control	374	489	553
0.4	378	484	536
0.8	371	466	527
1.6	375	320*	354*

Females - Mean Body Weight (gm)

	Week of Observation		
	0	7	14
Dose Group (ppm)			
Control	221	293	337
0.4	220	277	312
0.8	218	278	312
1.6	220	248*	274*

* - Statistically significant as compared to controls

Many of the hematology and serum chemistry parameters were abnormal for rats of the 1.6 ppm group, probably because of their generally debilitated condition. Changes in hematology, serum chemistry, and urinalysis noted for male or female rats of the 0.4 and 0.8 ppm groups were an increased mean corpuscular volume, increased erythrocyte count, decreased albumin concentration, decreased glucose concentration, and

decreased urine volume. No concentration-related changes in hematology, serum chemistry, or urinalysis were observed in mice exposed to 0.4 or 0.8 ppm.

At necropsy, the principal observations for rats of the 1.6 ppm group which either died or were humanely killed at week 14 included a color change of the lungs (congestion) and emphysematous lungs. For mice which died, pulmonary congestion and alopecia were the principal observations. The lung was the only organ for which biologically significant organ weight changes occurred. Absolute and/or relative (to either body or brain weight) lung weight values were increased for rats of the 1.6 ppm group and female mice (not statistically significant) of the 0.8 ppm group. For rats and mice which died on study, histopathologic lesions generally occurred throughout the entire respiratory tract. In the nasal cavity the lesions included necrosis, ulceration, squamous metaplasia, and inflammatory changes; necrosis and inflammatory changes generally occurred in the larynx and trachea; pulmonary changes included congestion, hemorrhage, necrosis, inflammation and in several animals, bronchiolar submucosal fibrosis.

Microscopic Nasal Cavity Incidence Summary
Animals Sacrificed at Week 14

Species: Rat	0 (Control)	0.4 ppm	0.8 ppm	1.6 ppm
Sex: Male/Female				
Total Number Examined	10/10	10/10	10/10	7/10
Examined, Unremarkable	8/10	0/0	0/0	0/0
Rhinitis	2/0	10**/10**	10**/10**	7**/9**
Ulcerative Rhinitis	0/0	0/0	0/0	3/1
Squamous Metaplasia	2/0	10**/10**	10**/10**	7**/9**
Mucus in Nasal Cavity	0/0	2/1	5*/10	6**/7**
Degeneration, Olfactory Epithelium	0/0	0/0	2/0	5**/1

Species: Mouse	0 (Control)	0.4 ppm	0.8 ppm	1.6 ppm
Sex: Male/Female				
Total Number Examined	10/10	9/10	8/8	2/0
Examined, Unremarkable	10/8	0/0	0/0	0/0
Epithelial Degeneration and Necrosis	0/0	7**/0	1/0	0/0
Acidophilic Droplets, Mucosal Epithelium	0/2	9**/10**	8**/8**	1/0
Rhinitis	0/0	7**/9**	8**/8**	2**/0
Mucus Accumulation In Cavity	0/0	1/5*	2/7**	2*/0
Squamous Metaplasia 0/0	0/9**	8**/8**	2**/0	
Cytoplasmic Vacuolization	0/0	0/0	0/2	0/0
Necrotic Rhinitis	0/0	0/0	0/1	0/0

* - Significantly Different From Control Group at 0.05
** - Significantly Different From Control Group at 0.01

In conclusion, mice and rats exposed to vapor TMXDI for up to 13 complete weeks had evidence of toxicity at all exposure concentrations. A no-observable-effect-level was not established for either species, although the incidence, severity, and depth of histologic lesions within the respiratory tract generally decreased with decreasing exposure concentrations. There

were no significant lesions noted in reproductive organs that could be attributed to exposure to TMXDI.

Test condition : This study was designed to assess the toxic effects of TMXDI when administered by inhalation as a vapor to groups of rats and mice. During non-exposure periods, water and food were available to the animals ad libitum. Food and water were withheld during exposures. Each group, (10/sex), was exposed for 6 hours per day, five days per week, for thirteen weeks at target concentrations of 0.4, 0.8 and 1.6 ppm. Temperature and relative humidity measurements were generally recorded 12 times per exposure. Cage placement within the exposure chamber was changed weekly in a predetermined manner to compensate for any possible variations in chamber exposure conditions.

Vapor was generated from a metered syringe pump connected to an electrically heated, vertical glass evaporator. Material passed through the evaporator facilitated by heated compressed air. The evaporator temperature was maintained at a specific range to vaporize the material. Gravimetric analysis was conducted to ascertain if any aerosol was being inadvertently generated. There was no indication of aerosol being present. Particle size distribution was measured 3 times during week 1 and once a week thereafter (except week 4). No mass distribution was calculated since there was no indication of aerosol being generated. Exposure levels were monitored 3x per day by HPLC.

During exposure, physical observations for abnormal signs were recorded on a group basis. Preceding and following each exposure observations were recorded individually. Prior to the first exposure and following exposure the eyes of all rats and mice were examined ophthalmically. All animals were weighed prior to first exposure and then once weekly thereafter. Serum chemistry and hematological evaluations were performed on blood from all surviving rats and mice. The following hematologic parameters were measured or calculated: leukocyte count, erythrocyte count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and platelet count. Serum clinical chemistry analyses were performed as follows: glucose, urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, total protein, albumin, globulin, total bilirubin, direct bilirubin, indirect bilirubin, gamma-glutamyl transferase, calcium, phosphorus, sodium, potassium and chloride. Urinalysis was performed on urine of all surviving animals at end of study. The following urinalysis parameters were measured or assessed: volume, color, turbidity and osmolality. Semiquantitative measurements were made on urine pH, protein, glucose, ketone, bilirubin, blood and urobilinogen. Necropsy and histopathology was performed on all animals on the study. The brain, liver, kidneys, lungs, and adrenal glands from all surviving animals and the testes from all male animals were weighed at necropsy and statistically compared to those of control animals.

The following reproductive tissues were examined at necropsy with lesions as noted.
Female mice: Cervix, vagina, ovaries (0.8 ppm: 2 mm clear cysts, bilateral), vulva, oviduct, ureter, uterus (control: bilateral dilatation/distention), mammary glands
Male mice: Prostate, testes, penis, mammary gland, epididymides, ureter, coagulating gland, seminal vesicle
Female rats: Cervix, vagina, ovaries, vulva, oviduct, ureter, uterus, mammary glands
Male rats: Prostate, testes (control: size decrease, bilateral, ½ of normal), penis, mammary gland, epididymides, ureter, coagulating gland, seminal vesicle.

During non-exposure animals received food and water ad libitum. Room

temperature (20 +/- 2 degrees C) was monitored and recorded twice daily. Relative humidity was maintained between 32-72%, monitored and recorded twice daily. During exposure the daily mean chamber temperature and relative humidity ranged from 18.5 to 28.9 degrees C and 24.9-59.1%, respectively.

Test substance : Respirable aerosol of TMXDI, CAS# 2778-42-9 (98% Isocyanic acid, m-phenylenediiso-propylidene in acetone), BRRC # 50-483 A to H.

Reliability : (1) valid without restriction
This study is assigned a reliability code of 1d according to the criteria established by Klimisch et al. (Regulatory Toxicology and Pharmacology 25: 1-5, 1997). Meets generally accepted scientific standards and is described in sufficient detail.

26.01.2005 (14)

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATIO N

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

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10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT